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A ROENTGENOLOGICAL STUDY OF THE METOPIC SUTURE[1]

by

Johan Torgersen

The persistent mediofrontal suture has called upon the interest of the anthropologist more than upon the interest of the radiologist. The reason for this may be that the suture has been considered as a normal variation. The radiologist is particularly interested in the possibility of making the diagnosis and to know if the suture has any clinical significance.

The metopic suture has been dealt with from the radiological point of view by ACKEN (1933). This author found an agreement between the frequency in the roentgenograms and in the statistics of the anatomists, a result indicating that the metopic suture is diagnosed in most cases in the roentgenogram.

There are a few investigations dealing with the clinical significance of the metopic suture. MATERNA and GERHARD (1936) compared anatomically the skulls of normal individuals and the skulls of patients from a psychiatric department finding an insignificantly increased frequency among the latter. This investigation does hardly permit any conclusions concerning a clinical significance of the metopic suture. BURSTEIN (1935) did not find any correlation between abnormalities of the brain and the meninges and the metopic suture.

HESS (1945) on the other hand proposes a »metopic syndrome». The persistent mediofrontal suture is the main trait of this syndrome, which has a variety of other manifestations, syndactyly and abnormalities concerning the relative length of the fingers, facial and cranial asymmetry and components of the somewhat vague conception of the status dys-

[1] Read at the Meeting of the Northern Association for Medical Radiology, June 10—12, 1949; submitted for publication Oct. 21, 1949.

From the Anatomic Institute, University of Oslo, Norway (Chief: Professor JAN JANSEN, M. D.) and the Roentgen Department of the University Hospital (Chief: Professor TORLEIF DALE, M. D.).

raphicus. HESS makes these statements on the basis of a material of 45 mentally defective individuals. The author does not give any information about the population from which this sample is taken. Presupposed that the sample is taken from a population of mentally defective individuals, and this is most probably the case, the data can hardly be considered as conclusive. In a sufficient number of such individuals the metopic suture probably will occur in the same percentage as in the normal population. The associated anomalies observed by HESS are so common in idiots generally that it is difficult to prove any relationship to the metopic suture. It is possible that the author is right maintaining that the metopic suture may have a clinical importance. However, from this paper one gets the impression that a pathologic metopic suture is a rather common occurrence, a supposition of which there is no evidence.

BOLK (1917) makes the statement that there is no correlation between hydrocephalus and the metopic suture. Thus the results so far concerning the clinical significance of the metopic suture is either negative or inconclusive.

Dealing with the metopic suture one has to separate the metopic suture reaching from the glabella to the bregma from the metopic fissure representing the remnants of the metopic fontanelle (fig. 1). The metopic suture is the persistent mediofrontal suture which ordinarily closes before the age of two years. The metopic fissure is a part of the anterior branch of the great fontanelle which may appear as a particular metopic fontanelle below the line between the frontal tuberosities. A skull may show a metopic fissure without the suture. However, the frequency of the metopic fissure is greater in cases of persistent metopic suture. The metopic fissure is a very rare occurrence. In 1,660 skulls at the disposal of the author the frequency is 0.54 per cent. The fissure is hardly possible to demonstrate in the roentgenogram unless it is exceptionally great. Such cases of great fissures are hardly possible to separate from the cases of non-fusion of the frontals as observed in cleidocranial dysostosis. In this anomaly are found both the suture, the fissure and the non-fusion of the frontals, a fact demonstrating the relationship between these anomalies of the frontal bone. All three anomalies have the same effect on the shape of the forehead and the face. The forehead tends to be broad with an increased curve of the frontal bone and bulging tuberosities. The root of the nose is low and broad and the distance between the eyes tend to be relatively great. This shape of the head and face is the consequence of the growth processes resulting from the late closure of the mediofrontal suture. This shape of the head is rather often observed also in individuals not showing a metopic suture. Is there any relationship between such skulls showing and not showing the metopic suture? How far is a more general conception of

the metopic skull justified? What are the characteristics and the clinical significance of the metopic skull?

Own Investigations

The present study deals with skulls in which the entire suture is present, not the supraglabellar part of the external table only. According to WELCHER (1862) the supraglabellar part has not the characteristic influence on the breadth of the skull.

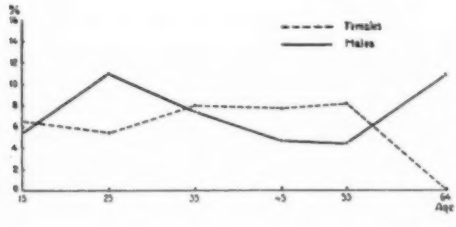
The supraglabellar part of the suture is of little interest to the radiologist because it is hardly visible in the roentgenogram. A series of roentgenograms of skulls from the anthropological institute showed that the completely persistent metopic suture is not visible in the roentgenogram if the inner table is closed and if there is no sclerosis along the suture. (Fig. 2.) The obliteration of the inner table takes place before the obliteration of the external table. In the stage between the closure of the tables the suture is not visible in the roentgenogram in many cases. For this reason it is not justified to compare anatomical and radiological statistics. The former gives information about the presence of the suture, the latter about the visibility of the suture in the roentgenogram. In 1,012 skulls from the medieval Oslo the frequency of the suture is 12.5 per cent. In 778 skull roentgenograms of the present population the frequency is 7.2 per cent. This does not show that the frequency has decreased in historic times, but probably how often the suture is visible in the roentgenogram.

The sex distribution has been discussed at some length. According to ESSEN MØLLER (1928) it is hardly possible to study this problem in skulls because the male metopic skull due to its slight sexual differentiation may be taken for a female skull. It is a characteristic trait of the metopic skull that the male skull approaches the female form. For this reason only a roentgenological study may clear up this problem.

As will be seen from the table and the graph the ratio between the sexes varies in the different age groups. The suture is seen relatively often in males between 20 and 30 years of age and in females between 30 and 50 years of age. The suture is seen even more frequently in males between 20 and 30 years of age than in earlier and later years. An χ^2 analysis of this curve, comparing the frequencies in males and females in the age groups 11—30 and 31—50 with the average frequency in both sexes in the age group 11—50, gives $\chi^2 = 7.54$ and by three degrees of freedom a probability of 0.05 that the sex difference in these age groups is due to chance. It may be concluded therefore that the difference between the sexes in the different age groups probably is significant.

The medio-frontal suture according to age and sex in roentgenograms

	Females			Males		
age in years	n.	m.	% m.	n.	m.	% m.
½—10	152	25	16.0	161	25	15.5
11—20	61	4	6.5	56	3	5.4
21—30	109	6	5.5	109	12	11
31—40	125	10	8	122	9	7.4
41—50	91	7	7.7	106	5	4.7
51—56	37	3	8.1	45	2	4.4
57—70	30	0	0	37	4	10.8
21—70	392	26	6.6	319	22	6.9



These findings indicate the processes taking place in the obliteration of the suture. Concerning the findings in the males they are in accordance with the observations of LASSILA (1922) and TODD and LYON (1924) that the suture start to close in males between the 20th and the 30th year. Regarding the findings in females they are in accordance with the statement of FREDERIC (1910) that the sutures obliterate later in females and with the statement of LASSILA that the closure in females nevertheless is accomplished at an earlier age due to the rapid progress of the processes in closure in females when first started. In old age the suture closes in males in which the suture for some reason has failed to close in earlier years.

The reason why the suture is more visible in some age groups than in others may be seen in the skull from the menopause, fig. 3. In this skull is seen a remarkable sclerosis along the suture producing the necessary roentgenographical contrast to make the suture visible. As will be seen the hyperostosis of the frontal bone which is common in this age in females is particularly prominent along the metopic suture, confined to one half of the bone. The hyperostosis and the processes in the obliteration of the metopic suture in this individual are apparently related processes. Most probably the suture shows about the same frequency in the sexes.

There is no evidence that the metopic suture behaves in any other way than the other sutures with regard to closure. According to TODD and LYON the closure of the different sutures and parts of the

Fig. 1. Skull of a cretin showing the metopic suture and fissure, a great interorbital breadth and a metopic forehead and face.

Fig. 2. Skull showing a completely patent metopic suture in the external table not demonstrable in the roentgenogram.

Fig. 3. Skull of a 44-year-old woman illustrating the relationship between the processes in suture closure and frontal hyperostosis.

Fig. 1.

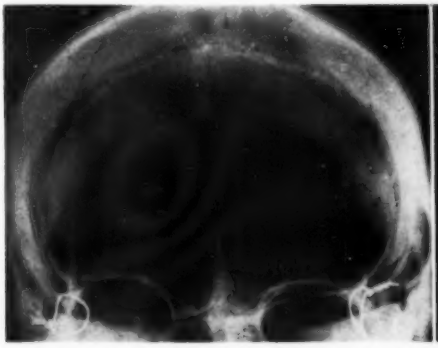


Fig. 2.

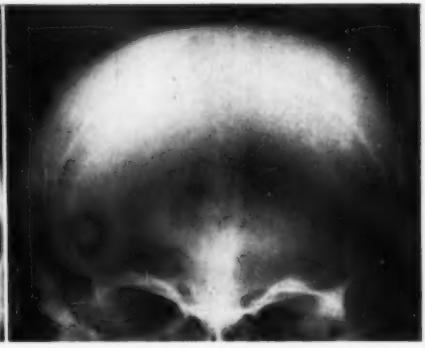


Fig. 3.

sutures have their own rhythm. There is no greater difference between the sagittal suture and the metopic suture than between the different parts of the sagittal suture.

The fact that the metopic suture in the roentgenograms shows about the same frequency in the age group 57 to 70 as in the age group 11 to 20 shows the correctness of the statement of WELCKER that the sutures generally close late in the metopic skull. The metopic suture is an indicator of a predisposition to late closure of the sutures and to the persistence also of other abnormal sutures expressing itself in the frequent occurrence of suture bones in the metopic skull and in an increased variability of the sutural pattern.

The fact that the frequency of the metopic suture does not decrease gradually with increasing age after two or three years of age shows that

Fig. 4.

Fig. 5.

Fig. 4. Skull of a cretin showing a metopic suture, a broad forehead and small frontal sinuses.

Fig. 5. Roentgenogram illustrating the apparent obliqueness of pictures in which the metopic suture deviates from the midline. A fracture in the suture can not be excluded.

there is a fundamental difference between the metopic and non-metopic skull. It is not simply a question of ossification rate. If this was the case one had to expect that the suture closed earlier in girls who show a rather advanced ossification compared with the boys.

If the metopic suture tends to late obliteration as in congenital myxoedema the tendency to late obliteration concerns the other sutures as well. The shape of the forehead and face is established in the period in which the mediofrontal suture is present. Even a slight delay in the obliteration may influence the shape of these parts of the skull. This is probably the cause of the shape of the forehead and face in cretins which may serve as an illustration of the metopic skull without any persistence of the metopic suture. Also the frontal sinuses are small in congenital myxoedema in the same way as in the persistent metopic suture.

In eight cases of congenital myxoedema in individuals above eight years of age the suture was found to be present in four of them. One of these was a boy 17 years of age (fig. 4). The sclerosis along the suture and the great gap of the suture in the inner table in this case indicate that bone is heaped up along the suture. The picture is most probably the radiological expression of what TODD and LYON (1925) call »lapsed union». In these cases no obliteration of the sutures is taking place, due to the heaping up of the bone along the suture.

The picture is so characteristic that it is improbable that this combination of cretinism and the persistent metopic suture is due to chance. This is even more improbable considering the observation of WELCKER of a metopic suture and fissure in a 40 years old cretin (fig. 1). This skull shows the characteristics of the metopic skull in a remarkable degree. FISCHER (1918) observed the metopic fissure in a 40 year old cretin. The observations show that the metopic suture and fissure probably have a tendency to persist in congenital myxoedema, not only to late obliteration.

The frequency of the suture was not increased in 26 cases of hydrocephalus a finding confirming the statement of BOLK that there is no correlation between hydrocephalus and metopism.

In 66 mentally retarded children below five years of age the suture was observed in 18 per cent, certainly not more than in other children. VOGT (1867) observed the suture in a microcephalic idiot, HESS reports to have seen the suture in mongolism. In 530 skull roentgenograms from the neurological department of the university clinic the skulls with a metopic suture did not show a preference for any particular pathologic condition. The frequency of the metopic suture in these roentgenograms is about 7 per cent and not greater than expected. In 313 skull roentgenograms of children below 10 years from the children's department the frequency is about 15 per cent and not greater than expected. With the one exception of congenital myxoedema there is no evidence in this material of a positive or negative correlation between the metopic suture and maldevelopment or disease. The data show that the metopic suture has a clinical significance only in rare cases.

The metopic suture deviates more often to the right than to the left of the midline. In 69 presumably female skulls the suture deviated to the right in 25 cases, to the left in two cases. In 61 male skulls the corresponding figures were 23 and 4 respectively. For this reason the radiologist may get the false impression that a correct frontal picture is somewhat oblique (Fig. 5). A pronounced asymmetry of the facial skeleton was observed in two skull roentgenograms. This may be due to chance. The metopic skulls from the anatomical department did not show any remarkable asymmetry. Due to the asymmetry of the suture the radiologist may be inclined to diagnose a fracture. In fact it may be difficult to decide even anatomically whether there is a fracture in the suture. Besides the characteristic shape these skulls show several other peculiarities. The frontal sinuses are small (ROCHLIN and RUBASCHEWA, 1934). In roentgenograms of 62 metopic skulls in the present study the frontal sinuses were absent in the squama in 24 per cent. In 400 non-metopic skulls the sinuses were absent in 5 per cent. The sep-

tum between the sinuses on the two sides is broad separating them completely.

The superciliary ridges are slightly developed and the bones are rather thin in the metopic skull. ROCHLIN and RUBASCHEWA conceive of this skull as the opposite of the acromegalic skull. In 10 cases of acromegaly I found a metopic suture in one case. Even if the number is small the finding indicates that there is whether a positive, nor a negative correlation between acromegaly and the metopic suture. The frontal sinuses are small in metopism, generally large in acromegaly. However, there is no simple relationship between acromegaly and the size of the frontal sinuses. In some cases the frontal sinuses are large, in other cases of average size. The thickening of the bone may affect either the internal or the external table and the thickening of the bone may or may not be associated with an increase in the size of the frontal sinuses. It is rather obvious that other factors than the hormons are essential to the manifestations of the disease. Probably the individual variability in this respect is due to the genetically determined reactivity of the tissues of the forehead. As there are generally no signs of an abnormal function of the pituitary in individuals with metopism besides the peculiarities of the skull it is reasonable to look upon the shape of the skull and the metopic suture as expressions of the inherited characteristics of the reactivity of the tissues of the forehead and facial skeleton. The metopic skull is not the opposite of the skull in pathological hyperpituitarism. The metopic skull and the typical acromegalic skull represent extremes concerning the reactivity of the tissues to the growth hormones of the pituitary. This inherited reactivity of the tissues of the frontal bone is probably the explanation of the experience that acromegalic traits are rather common in the family of individuals showing pathological acromegaly. There is evidently a central and peripheral factor in the development of the frontal bone the latter being predominant in the metopic skull. The pituitary component in cretinism may partly be responsible for the metopic suture in these cases.

As known the sinuses are small in atrophic rhinitis. These individuals may have the characteristic face seen in the metopic skull with the bulging forehead and the low broad root of the nose. In 12 cases of atrophic rhinitis the metopic suture was present in 2 cases. The figures are too small to be conclusive.

In previous studies the author has represented data which are rather good evidence that the shape of the respiratory part of the face and the forehead and the pneumatization of the frontal bone depend on a complex of genes which also influence the development of the lungs. The shape of the face in atrophic rhinitis is seen also in cases of hereditary ectodermal dysplasia in which atrophic rhinitis is one of the manifesta-

tions (KNORRE, THANNHAUSER). This fact reveals the existence of genes influenzing the development of the respiratory part of the skull and the upper respiratory tract. This shape of the skull is further seen in cleidocranial dysostosis which behaves as a dominant anomaly.

In a systematic study of visceral inversion the author observed a family in which the metopic suture behaves as a recessive trait. This is the first observation demonstrating that the metopic suture is hereditary in particular cases. The metopic suture in this family is on the borderline between a normal and a pathological feature. Some of the members of this family showed only a metopic suture. Other members showed associated anomalies, one of them situs inversus and a furrowed tongue, another a furrowed tongue and twisted teeth. The father and two sons showed spina bifida occulta. Cleft palate occurred on both the maternal and paternal side. The anomalies of the facial skeleton, the tongue, the teeth and the viscera depend probably on the manifold effect of genes which in other cases cause a metopic suture. Two of the members of the family had severe symptoms from the nose. The findings in this family will be dealt with in detail elsewhere. The findings represent a variety of the traits of the metopic skull, and of cleidocranial dysostosis, and of the manifestations of the hereditary factors influencing the development of the respiratory part of the skull and the upper respiratory tract.

The relationship to cleft palate and to the asymmetry of the viscera in this family is evidence that the metopic suture is influenced by the factors determining the symmetry of the organism. Cleft palate and the metopic suture are in themselves manifestations of growth differentials in relationship to the midline. Probably for this reason both cleft palate and the metopic suture show regular deviations from the midline.

The results of the present study are in conformity with those obtained by the experimental investigations of TROITZKY concerning the factors influencing the sutural pattern of the skull. The experiments showed that the place of the sutures is determined by the connective tissue underlying the bone and by factors outside the skull which integrate the development of the brain, the braincase and the organism. The data of the present study indicate that the inherited reactivity of the face and the forehead to the hormones of the pituitary and the genetic factors in symmetry play an important rôle in these developmental processes.

SUMMARY

The metopic suture is a normal variation. There is possibly a relationship to cretinism. The frontal sinuses are small. The skull is relatively thin and the sutures close rather late. The suture behaves as the other sutures with regard to closure showing the same sex differences. The suture is not visible in the roentgenogram if the inner table is closed and if there is no sclerosis along the suture.

ZUSAMMENFASSUNG

Die metopische Naht ist eine normale Variation. Es besteht wahrscheinlich eine Korrelation zum Kretinismus. Die Stirnhöhlen sind klein. Der metopische Schädel ist dünn und die Nähte schliessen sich spät. Die Naht verhält sich wie die anderen Nähte bezüglich der Obliteration und zeigt in dieser Hinsicht dieselben Geschlechtsverschiedenheiten. Die Naht ist im Röntgenbilde nicht sichtbar wenn die Innenfläche geschlossen ist und keine Sclerose vorhanden ist.

RÉSUMÉ

La suture métopique est une variation normale. Il y a peut-être une relation à la myxœdème congénitale. Les sinus frontaux sont petits. Le crâne est relativement mince, et les sutures se referment tard. La suture se comporte comme les autres sutures à l'égard de la fermeture, montrant les mêmes differences sexuelles. La suture n'est pas visible dans le roentgenogramme si la lame intérieure est fermée et s'il n'y a aucune sclérose le long de la suture.

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FROM RADIUMHEMMET, STOCKHOLM, SWEDEN (HEAD: PROFESSOR E. BERVEN)

SPONTANEOUS REGRESSION OF PLEURAL CARCINOSIS IN BREAST CANCER[1]

Report of a Case

by

Bengt A. Nohrman, M. D.

In a series of breast cancer studied by the writer,[2] there were 767 cases of radical mastectomies. Of these cases 4.6 per cent developed metastases to the pleurae within 5 years of the operation, and still another 4.5 per cent developed metastases with the same localization during the following 5-year period. Pleural carcinosis was localized to the operated side of the thorax in 65 per cent of the cases, to the opposite side in 20 per cent and was bilateral when the diagnosis was made in 15 per cent. Only the cases without simultaneous pulmonary metastases have been regarded as pleural carcinosis. The diagnosis was established through the finding of a rapidly growing exudate, containing tumour cells.

In all there are 35 cases of pleural carcinosis and of these six or 17.1 per cent were alive one year after the diagnosis was established. After two years only one patient survived, *i. e.* 2.9 per cent, and only died during the fifth year of observation. In this last case the disease shows a remarkable course, and therefore it has been considered of some interest to report this case, received at Radiumhemmet in 1936.

Record no. 7673/1936. A woman, aged 46 years. — The patient's grandmother died of breast cancer. Menarche at 12 years of age; menopause in connexion with an operation for benign tumour of the uterus nine years ago. No childbirths or abortions.

Since 1 ½ years she had noticed *a tumour in the left breast*. Besides that she had always been in good health.

Status at the admission on the 27th of October 1936: General conditions good. — In the upper medial half of the left breast a tumour was found, measuring 4 × 5 cm. The skin was fixed to the tumour and the nipple was retracted. No adenopathia was palpated in the axilla.

[1] Submitted for publication, Nov. 5, 1949.

[2] Acta radiol., suppl. 77.

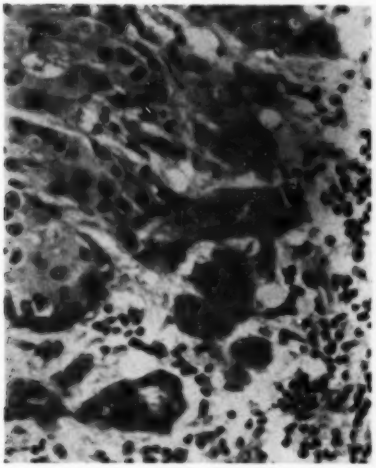

Fig. 1.

Fig. 2.

Fig. 1. Section of primary breast tumour (1936). Scirrous adenocarcinoma (× 260).
Fig. 2. Section of pleural nodule (1944). Metastases from the tumour in fig. 1 (× 190).

The patient received usual pre-operative roentgen irradiation and radical mastectomy with exaeresis of the axilla was performed on the 24th of November 1936. Microscopical examination[1] showed scirrous adenocarcinoma with metastases in one lymph node from the axilla (Fig. 1). After the operation post-operative irradiation was given.

In March 1937 a *tumour* was found *in the right breast*. This tumour was considered to be a cyst or possibly a carcinoma. The patient was very nervous, and thus simple mastectomy was performed without preceding irradiation. Microscopial examination showed fibroadenomatosis without signs of malignancy.

After the last operation the patient was free from symptoms for 6 $^1/_2$ years or until December 1943, when she developed *pleural exudate on the right side*. On the 3rd of January 1944 thoracoscopy was performed in Sabbatsbergs Sjukhus. The findings are described as follows:

After tapping 1,300 ml fluid with a colour like dark beer, there were seen a great number of tumours both on the parietal pleura and on the diaphragm. The tumours were of a size up to that of a bean. In the parietal pleura they were arranged in lines corresponding to the ribs. A smaller number of such tumours were also found on the surface of the lung. A specimen was taken from one of the latter. — Microscopical examination showed metastases from a carcinoma of the same type as was found in the left breast in 1936 (Fig. 2).

No irradiation or hormon treatment was given. The exudate, however, disappeared spontaneously after a couple of months and the patient did not return for follow up examination until June 1946 when she was in good general conditions and showed no signs

[1] All microscopical examinations have been carried out by professor O. REUTERWALL, the Radio-Pathological Institute of Radiumhemmet.

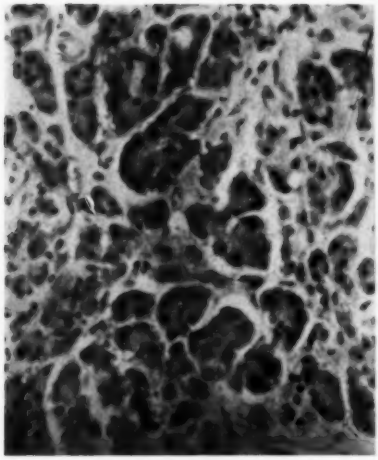

Fig. 3.

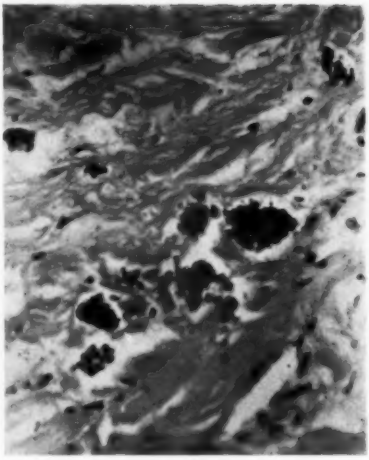

Fig. 4.

Fig. 3. Section of ventricular tumour at post-mortem (1948). Metastases from the tumour in fig. 1 (× 260).

Fig. 4. Section of right pleura at post-mortem (1948). Necrotic, atypical cells and induration of connective tissue (× 260).

of cancer. Roentgen examination of the thorax only showed old pleural changes, corresponding to the former exudate.

Then the patient was free from symptoms until July 1947 or a little more than 3 1/2 years after the thoracoscopy, when a *hard node* was found *in the right axilla, i. e.* on the opposite side of the tumour and on the same side as the pleural exudate. After preoperative irradiation exaeresis of the axilla was performed in August 1947. Microscopical examination again showed metastases from a carcinoma of the same type as was found in the breast in 1936.

The patient never recovered fully after this last operation, and thirteen months later she developed a complete ventricular retention. She was admitted to the surgical department of Karolinska Sjukhuset and laparotomy was performed. An extensive tumour infiltration of the ventricle was found and there were also metastases in the liver. No intervention was performed. — The patient died on the 21st of September 1948.

A *post-mortem* was performed. *Metastases* from a carcinoma of the same type as before were found in *pleurae, liver, omentum, mesenterium and ovaries*. Also the *ventricular tumour* was of metastatic origin (Fig. 3). Microscopical examination of the *right pleura* showed besides metastases also limited areas, containing necrotic, atypical cells, certainly of cancerous origin; around these areas there were metastases. According to the pathologist these findings from the pleura show that the metastases here at some occasion underwent a regression with calcification and induration of connective tissue (Fig. 4).

The development of the disease in this case presumably has been that the primary tumour in the medial half of the left breast has devel-

oped metastases to the parasternal nodes. Later on there has occurred a secondary spreading to the right pleura where the metastases, however, underwent a spontaneous regression and the patient was free from symptoms for more than three years. Then there occurred another dissemination of metastases wich lead *ad exitum*.

SUMMARY

A case of breast cancer is described with microscopically verified pleural metastases. The metastases underwent spontaneous regression and the patient remained free from symptoms for 3 $^1/_2$ years.

ZUSAMMENFASSUNG

Es wird über einen Fall von Brustkrebs mit histologisch bestätigten Metastasen in der Pleura berichtet. Die Metastasen gingen spontan zurück, und die Kranke blieb für 3 $^1/_2$ Jahre symptomfrei.

RÉSUMÉ

Un cas de cancer du sein avec des métastases de la plèvre est rapporté. Les métastases, verifiées par examination histologique, subirent une régression spontanée et la malade restait sans symptômes pendant 3 $^1/_2$ ans.

6th INTERNATIONAL CONGRESS OF RADIOLOGY

LONDON, 1950

A Reminder

A copy of the Preliminary Programme, together with the necessary forms for completion, has been sent to all members of radiological societies throughout the world. All those planning to attend are urged to register as Members of the Congress as soon as possible.

There are three classes of members: Full Members (including Junior, for those under 30); Associates accompanying Full Members, and Scientific and Technical Associates. All are reminded that a higher fee will be charged for registrations received after April 1st.

Members wishing to read papers must notify the Secretary-General not later than February 15th, and an abstract should reach him by April 1st. Those who have a scientific exhibit to offer must also send details by February 15th.

Application to join one of the tours of Great Britain and Ireland which are being organised for the week following the Congress must be received by February 15th.

All communications should be sent to the Secretary-General, 6th International Congress of Radiology, 45 Lincoln's Inn Fields, London, W. C. 2.

Additional copies of the Preliminary Programme can be obtained from the same address on request, stating the language in which it is desired.

FROM THE LONDON HOSPITAL, PHYSICS LABORATORY, LONDON, E. 1, ENGLAND

AN IMPROVED DOSE CALCULATOR FOR LINEAR RADIOACTIVE SOURCES[1]

by

L. A. W. Kemp, B. Sc., F. Inst. P.

Introduction

A linear radium source dose calculator for screened sources described earlier (1) (2) has now had considerable use, and modifications and additions to the original scheme to provide greater facility and speed of operation have inevitably suggested themselves.

The calculator constitutes essentially a scale model reproducing the geometry of the source, relative to the point at which the dosage rate is to be calculated. (The source may consist of up to 3 screened components in tandem, not necessarily of the same linear activities.) The position of the source relative to the point at which the dosage rate is required may be varied at will, by means of direct reading distance scales and convenient propelling mechanisms. In its new form the calculator indicates the actual dosage rate in roentgens per hour on a microammeter fitted with a special scale. Thus, once the instrument has been set up for the study of a given source (or tandem of sources), all that the operator has to do is to position correctly that part of the model representing the source in relation to the series of points at which the dosage rate is required, and note down the answers shown on the meter. In fact, the instrument simulates a radioactive source, the strengths and lengths of whose components may be varied at will, combined with a direct reading dose meter for exploration of distribution. The operational procedure requires no mathematical skill, and at the London Hospital dose distribution calculations of relatively complex arrays, such as those associated with volume implants, have been left in the hands of radiography students working in the Physics Department as part of their

[1] Submitted for publication, Oct. 17, 1949.

training course. The new calculator has made possible not only the detailed study of individual treatments, but also the derivation of a comprehensive treatment scheme employing so-called »differentially loaded» needles throughout, which avoids the need of »crossing the ends» in the majority of plane implants and many volume implants. It is easily adaptable for different types of source, and the one constructed at the London Hospital is intended to cater not only for radium and radon but also for radioactive cobalt sources which it is hoped to bring into use shortly.

Theory of Calculator as Applied to Radium

Part of this has been dealt with in an earlier paper, but will be repeated here for the sake of continuity.

Let ϱ = mg. of radium per cm. (linear activity).
Let h = perpendicular distance from line of radium to P (point at which dosage rate is to be calculated). (Fig. 1.)
Let $f(\theta)$ (the screenage function) = fractional intensity reduction due to the screen, for radiation proceeding to P from an element dm in direction θ to normal.
Let k = a constant converting dosage rate to roentgens per hour.[1]

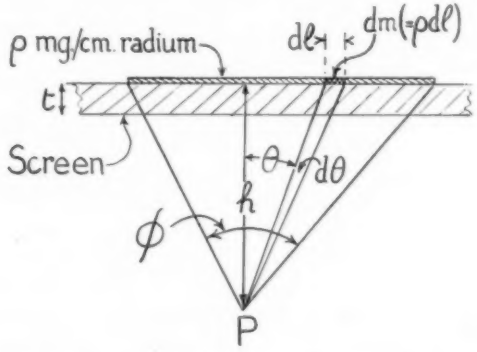

Fig. 1.

[1] Thus for 1 mg. of radium screened by 0.5 mm. platinum, dosage rate at 1 cm. may be taken as 8.4 roentgens per hour (3).

$$\therefore\ 8.4 = \frac{k \cdot 1\ (\text{mg.})}{1^2\ (\text{cm.})} \cdot \underset{0.5\ \text{mm Pt}}{f(0°)}$$

$$i.e.\ k = \frac{8.4}{\underset{0.5\ \text{mm Pt}}{f(0°)}}$$

Then the contribution to the dose rate at P due to element $dm\ (=\varrho dl)$ in direction θ to normal

$$= \frac{k(\varrho dl)}{h^2/\cos^2\theta} \cdot f(\theta) \text{ r/hour}$$

$$= \frac{k\varrho\, f(\theta)d\theta}{h} \text{ r/hour}$$

$$\therefore D \text{ (dosage rate at P)} = \frac{k\varrho}{h}\int_{\theta} f(\theta)d\theta$$

Certain considerations relating to $f(\theta)$ have already been given in one of the earlier papers (1944) (1) indicating the desirability of basing $f(\theta)$ on experimentally determined values.[1]

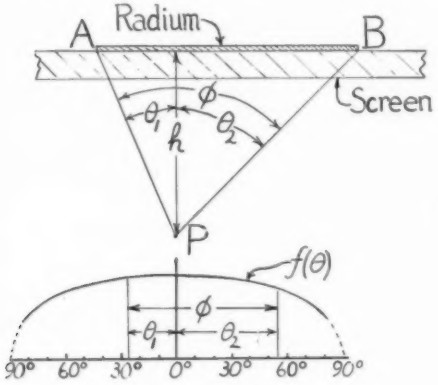

Fig. 2.

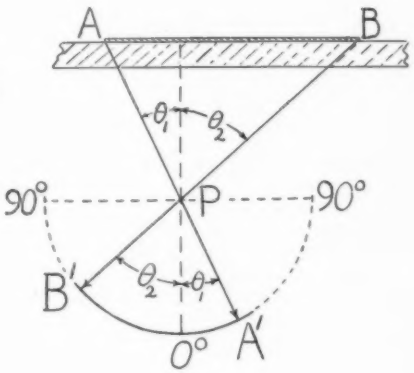

Fig. 3.

Suppose then that for a given thickness t of absorber, $f(\theta)$ has been suitably determined. Then a method is required of integrating $f(\theta)$ over any range such as ø (Fig. 2 — in which values of the function are indicated diagrammatically for angles of incidence approaching 90° on either side of the normal). The method employed is as follows. A thin strip of insulating material is cut to the shape of the area under the graph of $f(\theta)$ between limits approaching 90° on either side of the ordinate representing normal incidence. Resistance wire is then wound round the strip in such a manner that each half turn approximates to an or-

[1] I am indebted to Dr. J. READ for such data, based on a series of measurements using virtually unscreened radium as the source and lead as the absorbing material. Lead and platinum have sufficiently close atomic numbers to enable this data to be used directly for the determination of the relationship between absorption and thickness (and hence angle of incidence) for platinum.

dinate to the curve, the turns being regularly spaced and sufficiently close together for this approximation to be valid. The resistance of the wire between the two turns representing any chosen pair of ordinates will then be proportional to the integral of $f(\theta)$ between the limits represented by these ordinates, and the constant of proportionality can easily be determined by comparing actual values of the integral between selected limits (computed graphically) with the corresponding resistance values. Once this constant has been determined, the resistance between any pair of turns may be converted at once into the value of the integral of $f(\theta)$ between the corresponding limits.

In the actual instrument, the ends A and B (Fig. 3) of the active length of the source are marked by swivelled supports over which slide arms pivoted at P, the portions of the arms which extend beyond P carrying contacts at A′ and B′. The strip carrying the resistance winding can then be arranged in a circular arc centre P, in such a way that as AB is moved parallel to itself the turns with which A′ and B′ are in contact are always those corresponding to the ordinates which mark the limits of the range over which integration of $f(\theta)$ is required. For this to be achieved the radius associated with the middle turn (corresponding to normal incidence) must be perpendicular to the line containing A and B, and the radius of the arc into which the strip is bent must be such that the remaining turns are given their appropriate angular co-ordinates relative to P.

Suppose n is the constant of proportionality relating R, the resistance between any particular pair of ordinates on the screenage function resistance, to the corresponding value of $\int f(\theta)\,d\theta$ so that

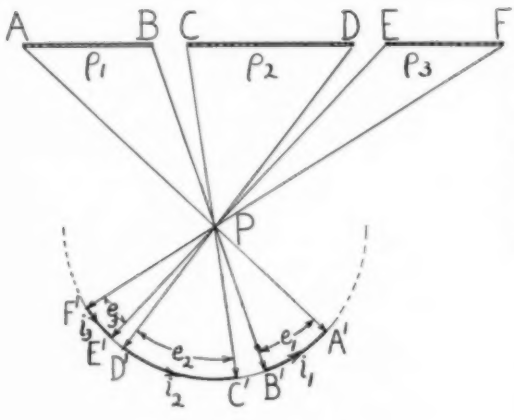

Fig. 4.

$$\int f(\theta)\,d\theta = \frac{R}{n}.$$

If then, i ampères is the value of a (constant) current fed to the pair of contacts A′ B′, and e volts the corresponding potential difference developed between them, then

$$R = \frac{e}{i}.$$

$$\therefore \int f(\theta)\,d\theta = \frac{e}{ni}$$

$$\& \; D = \frac{k\varrho}{h} \cdot \frac{e}{ni}.$$

For two or more sources AB, CD, EF ... in tandem (Fig. 4), of linear activities ϱ_1, ϱ_2, ϱ_3 ... mg/cm.,

$$D = \frac{k\varrho_1}{h} \cdot \frac{e_1}{ni_1} + \frac{k\varrho_2}{h} \cdot \frac{e_2}{ni_2} + \frac{k\varrho_3}{h} \cdot \frac{e_3}{ni_3} + \ldots$$

where i_1, i_2, i_3 ..... may have any (constant) values.

Suppose $i_1 : i_2 : i_3 \ldots$ be arranged to be as $\varrho_1 : \varrho_2 : \varrho_3 \ldots$ and that when $\varrho = 1$ the corresponding current $= I$. Then

$$i_1 = \varrho_1 I \quad i_2 = \varrho_2 I \quad i_3 = \varrho_3 I$$

$$\& \; D = \frac{k}{nI} \cdot \left[\frac{e_1 + e_2 + e_3}{h}\right]$$

$$= \frac{k}{nI} \cdot \frac{\Sigma e}{h}.$$

Σe may be obtained by connecting the intercepts A′ B′, C′ D′, E′ F′ ... in series as shown in Fig. 5.

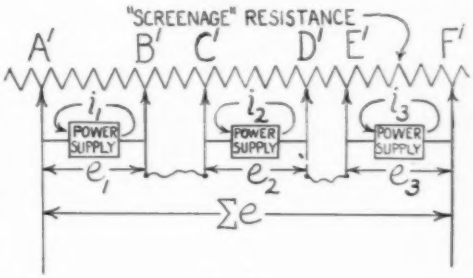

Fig. 5.

If the potential difference Σe is then applied to a resistance whose value is arranged to vary as h (the »h» resistance) (Fig. 6) which is always of sufficiently high value to ensure that it has no appreciable shunting effect on the resistances A′ B′, C′ D′, E′ F′ ... in which e_1, e_2, e_3 are developed, then we have

»h» resistance value $= shr$,

where

s = a constant[1] (equal to the »scale factor» of the instrument)

r = resistance per cm. of the »h» resistance,

h = *actual* value of the perpendicular from the source to P,

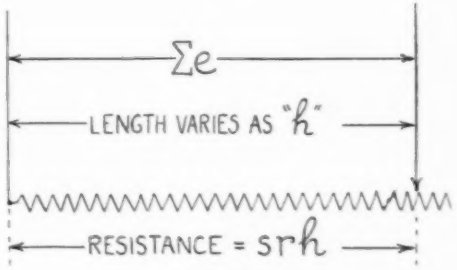

Fig. 6.

[1] In the instrument, the »h» resistance effectively commences at P and extends an adequate length in the direction of h. A contact on it, carried by the slide representing the line of the source, then intercepts a length which varies as h and is given by sh, where s, as mentioned above, is the scale factor of the »model».

and the current i' generated in this circuit is given by

$$i' = \frac{\Sigma e}{srh}$$

$$\text{whence } \frac{\Sigma e}{h} = sri'$$

$$\& \; D = \frac{k}{nI} \cdot sri' = \frac{ksr}{nI} \cdot i'$$

To recapitulate, in the expression $\frac{ksr}{nI}$,

k = a constant converting dosage rate to roentgens per hour,
s = the geometrical scale factor employed in the instrument,
r = resistance in ohms per cm. of the (linear) »h» resistance,
n = the constant of proportionality between resistance (in ohms) and $\int f(\theta)\, d\theta$ for the screenage resistance, and
I = the current in ampères chosen to represent a value of ϱ of 1 mg/cm.

Thus:

$$D = \text{constant} \times i'$$

and *it follows that a meter indicating i' can be provided with a linear scale calibrated direct in roentgens per hour.*

Practical Considerations

Electrical. The complete instrument circuit is shown in Figs. 7 (a) & 7 (b). For each source component (as already stated, the instrument caters for up to three) a power supply is required which will provide a sensibly constant current to the corresponding intercept on the screenage function resistance. It follows that the resistance of the power supply must be many times (of the order of 50 to 100) any resistance value which can be assumed by the intercept during the operation of the instrument. As constructed, the screenage function resistance has a total value of approximately 150 ohms, and each of the power supplies feeding the intercepts on it are resistance smoothed with a minimum resistance of 6,000 ohms.

In order to develop reasonable potentials (of the order of 1 volt) across the intercepts, 0.060 amp. was chosen as the value of I, the current corresponding to a value of ϱ equal to 1 mg/cm.

The three power supply circuits are so arranged that a meter (full scale deflection 75 mA) calibrated direct in *mg/cm. radium* (*i. e.* 0 to 1.25 mg/cm.) can be switched into each in turn when setting up the instrument. Coarse adjustment of the current provided by each supply

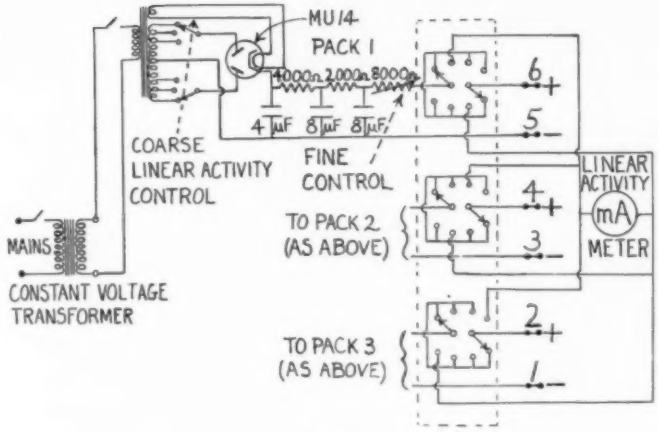

Fig. 7 a.

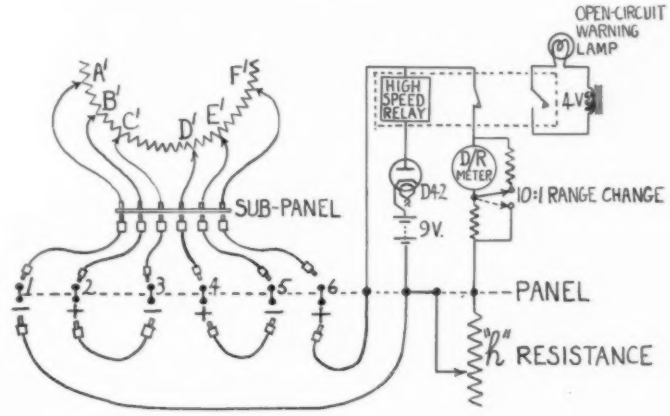

Fig. 7 b.

Fig. 7 (a), 7 (b). Circuit of direct reading linear radioactive source dose calculator.

is obtained by switched tappings on the transformer secondary which feeds the rectifying diode, and fine adjustment by a variable series resistance. All three supplies are fed from a constant voltage transformer to eliminate errors which might otherwise be introduced by fluctuations in mains voltage.[1]

[1] The supply of up to 75 milliamps. through a resistance of the order of 6,000 ohms requires some 450 volts. It is easily seen from Fig. 8 that should one of the contacts (A′ and B′) accidentally leave the screenage function resistance, a large voltage is ap-

Like the power supplies, the »*h*» resistance must also have a value which (even at the minimum »*h*» distance catered for) is very much greater than the values of the screenage function resistance intercepts. Two sets of direct reading distance scales are provided on the instrument, employing scale factors of 5 times and 10 times respectively, and as values of »*h*» at least down to 0.5 cm. must be catered for the »*h*» resistance must have a minimum length of 2.5 cm. A value of *r* (resistance per cm.) of approximately 2,500 ohms thus ensures that the »*h*» resistance value does not fall below about 6,000 ohms.

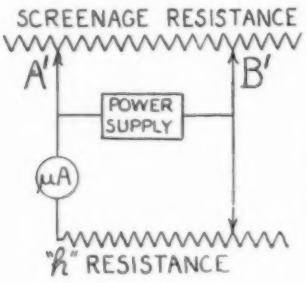

Fig. 8.

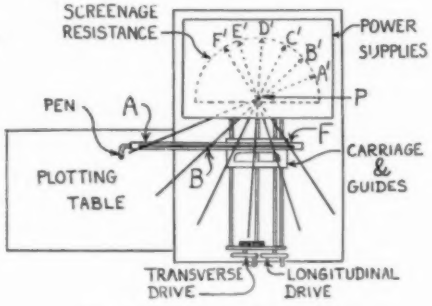

Fig. 9. Lay-out of calculator.

Mechanical. The swivelled supports A, B, . . . F. etc. (representing the source ends) (Fig. 9) can be clamped in any position along a slot in the top of a square section tube constituting what may be termed the transverse slide, movements of which convey the supports along a line containing them. This movement is obtained by a mechanical drive from a hand wheel at the front of the instrument, and by means of it the position (opposite the source) of the point at which the dosage is being observed may be varied at will. The transverse drive is so arranged that it also permits longitudinal movements of the carriage supporting the transverse slide, this carriage also being propelled mechanically by a hand wheel at the front of the instrument. By means of the longitudinal drive the perpendicular distance (from the line of the sources) of the point at which dosage rate is being calculated, *i. e.* h, can be varied over an adequate range. Both transverse and longitudinal movements,

plied to the microammeter circuit with the risk of damage to the meter. The maximum voltage applied to this circuit in normal operation is about 7.5. An overload cut-out device is therefore incorporated, consisting of a diode biased to 9 volts and put across the input to the microammeter circuit. When the voltage here rises much above 9, the diode takes sufficient current to operate a high speed relay which opens the meter circuit before the meter pointer has had time to reach full scale, and lights a warning lamp.

as well as the positions of the swivelled supports along the slot in the transverse slide, can be observed on direct reading scales indicating the equivalent distances in cm.

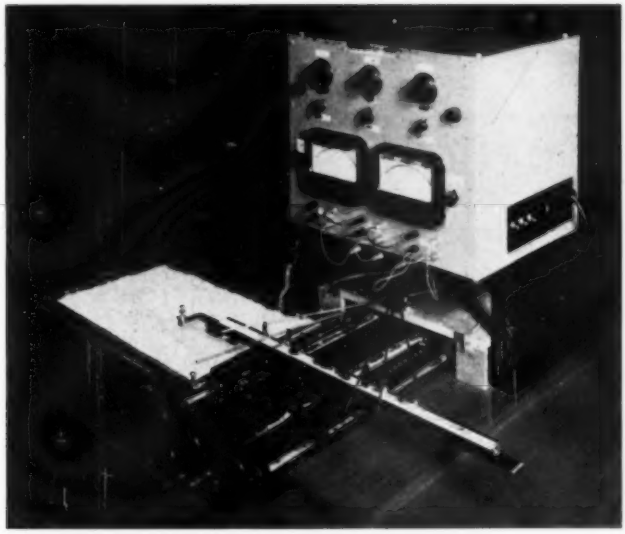

Fig. 10. General view of calculator.

General. A view of the instrument is shown in Fig. 10. It is seen that for the sake of compactness the 3 power supplies, current controls, linear activity meter, and dosage rate meter have been arranged as a single unit over the screenage function resistance. For convenience the interconnections between power supplies and the sliding contacts on the screenage resistance are effected by plug leads and sockets, the latter being situated at the lower part of the instrument panel.

Procedure

As already pointed out in an earlier paper, an instrument of this type has the fundamental advantage that the co-ordinates of points at which pre-selected dosage rates obtain may be found by *exploration*, thus eliminating the need to interpolate graphically to obtain isodose curves.

Examples:

(1) It is required to find the 30, 20, 15, 10, 7.5, 5, 4, 3, & 2 r/hr. dose rate lines in a plane containing a differentially loaded source consisting

of 3 contiguous components, all screened by 0.5 mm. Pt. The middle component is 1.5 cm. long and has a linear activity of 0.33 mg/cm., whilst the two end components are each 0.75 cm. long and have a linear activity of 0.67 mg/cm.

By means of one of the direct reading distance scales (on the transverse slide) four of the swivelled supports representing the ends of the

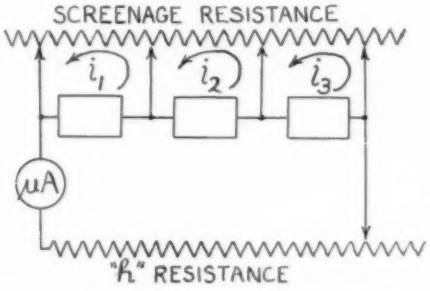

Fig. 11. General mode of connection of calculator in order to compute Examples 1 & 2.

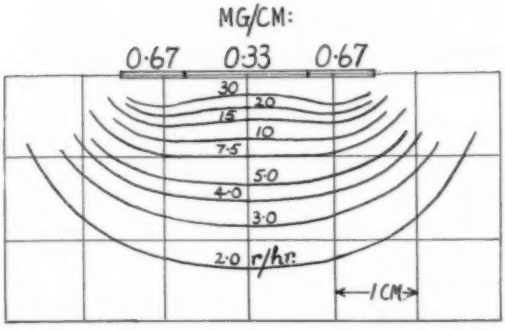

Fig. 12. Isodose curves round a differentially loaded 3 cm. active length source, as computed by calculator. Time taken: 40 minutes.

source components are set up at points along the slot, at intervals representing the lengths of the three components. The power supplies and screenage function resistance intercepts are then inter-connected as shown in Fig. 11. The linear activity meter is then switched into each supply circuit in turn and the coarse and fine controls set to provide the required linear activities for the three components. The mechanical movements provided are then used to bring the source close to the pivot representing P, with the latter on the perpendicular bisector through the source. The longitudinal movement only is then used to increase steadily the value of h, and as this is done the distances are noted at

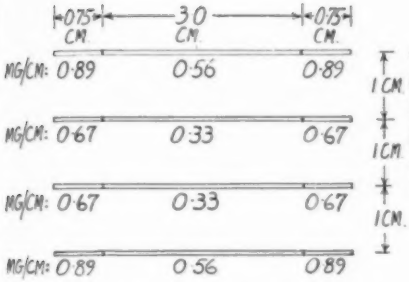

Fig. 13 (a). Lay-out of four 4.5 cm. differentially loaded needles as described in Example 2.

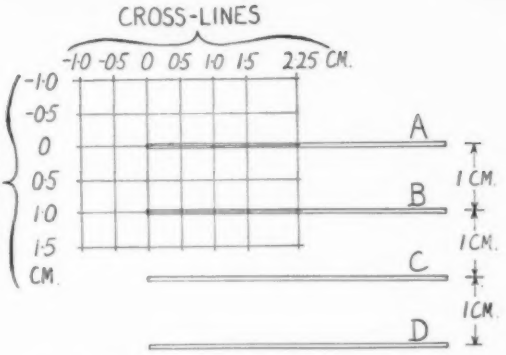

Fig. 13 (b). Scheme of points at which dose rates were calculated in Example 2.

which the required dosage rates are obtained.[1] This procedure is repeated for a series of lines (other than the bisector) perpendicular to the source. Isodose lines may then be plotted at once (Fig. 12). Total time taken for this calculation: 40 minutes.

(2) It is required to investigate the dose distribution in a plane 0.5 cm. from the plane containing four 4.5 cm. differentially loaded needles as shown in Fig. 13 a.

A series of lines is chosen in the plane considered, the lines being parallel to the needle directions. These lines are called »parallels». They are 0.5 cm. apart. Another series is chosen in the same plane, at right angles to the first series and (in general) 0.5 cm. apart. These are called »cross lines». A convenient nomenclature in each case is to denote a line at the edge of the nominal area treated (4.5 × 3 cm.) as a »0» line, giving plus or minus signs to the distances of the other lines from it, according to whether they lie inside or outside the treated area (Fig. 13 b). The intersections of these two sets of lines in the plane considered form a mesh of points at the corners of 0.5 cm. squares (apart from those involving the 2.25 cm. cross line), at each of which the dose rate contributions of each of the four needles are found, and then added to give

[1] A simple point plotter may be added to the instrument, making the procedure just described particularly straightforward. A stylus (electrical — working on a special recording paper — or ink) is fitted to the end of the transverse slide, and as the transverse and longitudinal movements take place, the positions at which the pre-selected dosage rates are found may be recorded direct on a sheet of paper under the stylus, the scale of the diagram obtained being the same as that employed on the instrument. This plotting table is seen to the left of the main instrument in Fig. 9 & 10.

Table 1

Mode of tabulation of calculator readings for Example 2.

Parallel	Source	h	Crossline						
			−1.0 cm.	−0.5 cm.	0	0.5 cm.	1.0 cm.	1.5 cm.	2.25 cm.
	A	1.12 cm.	3.30 r	5.00 r	7.20 r	8.10 r	9.90 r	10.20 r	10.30 r
	B	2.06	1.42	1.75	2.12	2.41	2.60	2.71	2.76
−1.0 cm.	C	3.04	0.93	1.07	1.22	1.33	1.41	1.46	1.48
	D	4.02	0.97	1.08	1.18	1.27	1.33	1.38	1.41
		Total:	6.62	8.90	11.72	13.11	15.24	15.75	15.95
	A	0.707	3.90	6.70	12.60	17.00	17.60	17.20	17.20
	B	1.58	1.79	2.36	3.08	3.70	4.00	4.20	4.20
−0.5	C	2.55	1.14	1.35	1.55	1.74	1.87	1.95	1.99
	D	3.54	1.15	1.29	1.43	1.54	1.66	1.72	1.76
		Total:	7.98	11.70	18.66	23.98	25.13	25.07	25.15
	A	0.50	4.00	8.00	19.40	28.20	27.10	25.80	25.40
	B	1.12	2.01	3.40	4.90	6.10	6.40	6.40	6.40
0	C	2.06	1.42	1.75	2.12	2.41	2.60	2.71	2.76
	D	3.04	1.37	1.58	1.80	1.98	2.12	2.20	2.28
		Total:	8.80	14.73	28.22	38.69	38.22	37.11	36.84
	A	0.707	3.90	6.70	12.60	17.00	17.60	17.20	17.20
	B	0.707	2.59	4.80	9.00	11.80	11.50	10.80	10.60
0.5	C	1.58	1.79	2.36	3.08	3.70	4.00	4.20	4.20
	D	2.55	1.71	2.00	2.33	2.62	2.84	2.99	3.07
		Total:	9.99	15.86	27.01	35.12	35.94	35.19	35.07
	A	1.12	3.30	5.00	7.20	8.10	9.90	10.20	10.30
	B	0.50	2.63	5.70	14.30	20.10	17.60	16.00	15.50
1.0	C	1.12	2.01	3.40	4.90	6.10	6.40	6.40	6.40
	D	2.06	2.07	2.57	3.20	3.80	4.20	4.30	4.40
		Total:	10.01	16.67	29.60	38.10	38.10	36.90	36.60
	A	1.58	2.55	3.60	4.70	5.50	6.10	6.40	6.50
	B	0.707	2.59	4.80	9.00	11.80	11.50	10.80	10.60
1.5	C	0.707	2.59	4.80	9.00	11.80	11.50	10.80	10.60
	D	1.58	2.55	3.60	4.70	5.50	6.10	6.40	6.50
		Total:	10.28	16.80	27.40	34.60	35.20	34.40	34.20

Mean dosage rate for treated area = *34.7 r/min.*

∴ Time for 6,000 r = *173 hours.*

the total dose rate at each point. Readings on the calculator may conveniently be tabulated as shown in Table 1. (A quarter of the area only is considered, since obviously the distribution is symmetrical about two axes at right angles.)

The mean dose rate for the *whole* plane may then be found, and the time for an average of say 6,000 r to the nominal treated area deduced. Graphical interpolation may then be employed to give isodose lines if required. The result is shown in Fig. 14. Time taken for this calculation

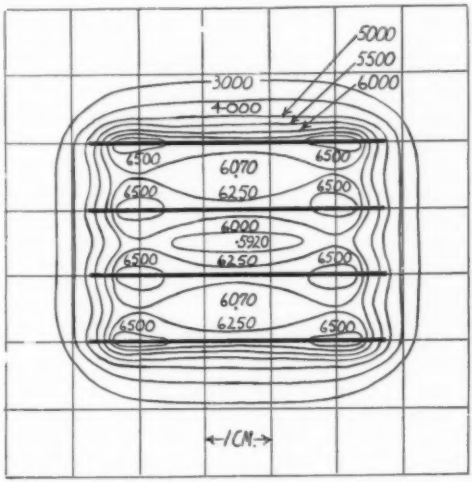

Fig. 14. Isodose curves in plane 0.5 cm. from plane of sources shown in Fig. 13 (a), as computed by calculator. Time for calculator readings: 50 minutes (see Table 1). Total time (including graphical work) 3 to $3^1/_2$ hours.

(including readings on calculator — 50 mins. — and graphical work etc.) 3 to $3^1/_2$ hours.

(3) Although no detailed example can be given here, it is to be emphasized that a direct reading calculator of this type is so rapid in use that cases requiring very irregular layouts of radium (which cannot be dealt with by Paterson-Parker rules, for example) may be considered *ab initio*. In this way relatively complicated irregular three-dimensional arrays can be surveyed in a few hours.

Appendix

Adaptation of Calculator for Linear Radioactive Cobalt Sources

Basically this merely requires a second screenage function resistance representing the values of $f(\theta)$ (for cobalt gamma rays) for the clinical screenage employed, together with additional scales engraved on the dosage rate meter. It is hoped to publish details at a later date.

Acknowledgements

The research work of this department is supported by the funds of the British Empire Cancer Campaign. The author also wishes to express his gratitude to Dr. FRANK ELLIS for his keen interest in the project, and his encouragement during the development of the instrument in its final form.

SUMMARY

An account of the theory and construction of a direct-reading screened linear radium source dose calculator is given. The instrument, which has been developed from a simpler one described in earlier papers, caters for a source having up to three components in tandem not necessarily of the same linear activities, and indicates the actual dosage in roentgens per hour on a specially calibrated microammeter. In fact it simulates a radioactive source, the strengths and lengths of whose components may be varied at will, combined with a direct reading meter for exploration of dose rate distribution. The operational procedure requires no mathematical skill. Examples of typical calculations are given.

ZUSAMMENFASSUNG

Ein Bericht über die Theorie und Konstruktion eines direkt ablesbaren Kalkulators für Dosen aus einem geschirmten linearen Radiumpräparat. Das Instrument, das aus einem einfacheren, früher beschriebenen entwickelt worden ist, besorgt die Bestimmung eines Präparates, das aus höchstens drei Komponenten nach einander besteht, die nicht unbedingt von denselben linearen Aktivitäten sein müssen. Ein besonders kalibrierter Mikroamperemesser gibt die wirkliche Dosis in Rœntgen per Stunde an. Das Instrument simuliert ein radioaktives Präparat, von dem die Stärke und Länge seiner Komponenten beliebig variiert werden können, ferner auch einen direkt ablesbaren Messer für Angabe der Dosisverteilung. Die Handhabung erfordert keine mathematische Fähigkeit. Beispiele von typischen Bestimmungen sind angegeben.

RÉSUMÉ

L'auteur donne les bases théoriques et indique la construction d'un calculateur à lecture directe pour les radiations filtrées d'une source linéaire de radium. L'instrument, qui a été développé en partant d'un autre, plus simple, décrit dans des publications antérieures, s'adapte à une source ayant jusqu'à trois composantes en tandem, non nécessairement des mêmes activités linéaires, et donne la dose effective en roentgens par heure sur un microammètre spécialement étalonné. De fait, il simule une source radioactive dont on peut à volonté faire varier les forces et les longueurs des composantes, en combinaison avec un dosimètre à lecture directe pour connaître la distribution des doses. L'utilisation de l'appareil n'exige pas de connaissances en mathématiques. Des exemples de calculs typiques sont rapportés.

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FROM THE RADIOLOGICAL DEPARTMENT OF THE ST. CANISIUS HOSPITAL, NYMEGEN, HOLLAND.

LONG REMISSIONS IN HODGKIN'S DISEASE[1]

by

J. Th. van der Werff, D. Sc., M. D.

In 1832 HODGKIN described the 7 cases, in which painless swelling of lymph-nodes, enlargement of the spleen, cachexia and fatal termination occurred together. We know now that these 7 patients certainly did not suffer from the same disease, but that probably 3 of them were victims of the illness we know now as Hodgkin's disease, malignant granuloma or lymphogranulomatosis, only diagnosed with certainty by the histo-pathological picture. This picture, characterized by the occurrence of Reed-Sternberg giant-cells, has transformed the lymphogranulomatosis into a sharply defined disease. One may even add that without this characteristic picture Hodgkin's disease would never have become such a well-defined disease, for the clinical as well as the other symptoms occurring, like temperature, enlargement of the spleen, pruritus, blood-picture etc. show all kinds of variations. If one reviews the very extensive literature, it can be noticed that practically all that can be investigated has been examined. Yet a great number of important questions remain unanswered. As for the etiology, all kinds of opinions have been expressed. That Hodgkin's disease might be a neoplasma, an inflammation, a combination of both, a systemic disease, a consequence of metabolic disturbances, each of which subdivided, finds supporters with arguments pro and opponents with arguments contra.

Also concerning treatment there is no unanimity up to now and again, if one reviews the literature (see HOSTER, DRATMAN, CRAVER and ROLNICK in Cancer Research, 1948), one becomes confused by the multitude of remedies advised: all kinds of chemo-therapeutics, from the old arsenic to the modern nitrogen-mustards, vaccino-therapy, surgery, radio-active substances and roentgen-rays. But if one considers what has been obtained by all these various treatments, one must conclude that up to now the treatment by roentgen-rays gives by far the best

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results. This does not mean that all other measurements are valueless. In very early cases surgery has booked some remarkable successes. Arsenic can perhaps support the roentgen-treatment, and the nitrogen-mustards have already received their place if irradiation is not possible or no more possible. But, if possible, roentgen-irradiation is, up to now, the treatment of choice. Yet even here there is no unanimity and the following various techniques are applied:

a. Local high-voltage roentgen treatment in fractionized tissue-destructive doses (O'BRIEN, RATKÒCZY etc.),

b. The same, followed by irradiation of other fields where non-observable foci are expected (GILBERT, JACKSON and PARKER, etc.),

c. The same, followed by general body-irradiation (MEDINGER and CRAVER),

d. Local high-voltage roentgen treatment in palliative doses (SLAUGHTER and CRAVER etc.),

e. Local moderately high-voltage roentgen treatment in palliative doses (DESJARDINS),

f. General body-irradiation (MARCHAL, MALLET and BELLIN).

The cause of this lack of unanimity is certainly to be found in the fact that

1. Hodgkin's disease is a relatively rare disease, which makes the number of cases in the various statistics always small.

2. The clinical pictures in each statistical series diverge in such a way that one can by no means speak of a homogeneous material.

Classification into acute, subacute and protracted cases (O'BRIEN), in forms with slow evolution, rapid forms and acute forms (GILBERT) as well as into paragranuloma, Hodgkin's granuloma and Hodgkin's sarcoma (PARKER and JACKSON) remains subjective to a high degree. The consequence is, that the statistics prove little as to the best way of treatment. Yet one can try to come to a reasonable judgement if one investigates the way in wich the best results have been obtained in individual cases. Of course, in those cases one only deals with forms in which the disease is in a rather early stage or has a relatively benign character, but the way of treatment will certainly have been of utmost importance for the good result.

First of all it is necessary to define what one has to understand by the best attainable result and of course this will be a survival-time as long as possible. But next to it there is another aim of equal importance and which has been defined so well by GILBERT: »Le but est d'obtenir des rémissions aussi franches et aussi longues que possible, donnant au malade, avec l'illusion d'une santé recouvrée, une entière capacité

de travail.» The fact that among the patients, treated in the author's hospital there are two, who already for more than 5 years have enjoyed clinical health, has occasioned the examination in the literature for the way in which such long remissions have been obtained elsewhere. It goes without saying that the number of such long remissions must be small, as they form only a small percentage of the total number of cases treated and so they only occur in communications of relatively large series. It strikes one directly that they are always obtained by that kind of treatment which aims at destroying the observable foci as completely as possible, while in a number of cases this treatment has also been extended to those regions where small, not yet observable foci are suspected. This method is the one which for years has been propagated by GILBERT and whose statistics also show the longest mean survival-times. In his report of 73 cases, published in 1939 there are 4 cases in which remissions of more than 5 years were obtained. With two of these cases even remissions of more than 10 and 13 years respectively occurred.

In a personal communication in this year concerning 4 very long survival-times of 11, 27, 18 and 20 years respectively, a third patient, a woman, has been free from symptoms now already 18 years, during which time she has given birth to three healthy children.

JACKSON and PARKER, who at the present time are using GILBERT's techniques, describe in their book a total of 213 cases, viz. 28 cases of paragranuloma, 133 of Hodgkin's granuloma and 32 of Hodgkin's sarcoma. In the first group, in which the disease has to be considered in its very early stage and in which it was limited to a single focus, surgery booked striking successes in a few cases, apparently by total destruction of the primary focus. With the first case, in which in 1920 dissection of the focus in the right supraclavicular region was done, further symptoms held off till 1939, when there occurred a relapse in the mediastinum. Thus a remission of 19 years. In a second patient, a paragranuloma at the right side of the neck was excised in 1910, whereafter there occurred a relapse in the same region in 1917, which was again excised. 19 years afterwards, in 1936, the same happened once more and since then the patient has been free from symptoms. It is probable that the same or even better results would have been obtained if the focus had been destroyed by roentgen irradiation, for in general it will be certainly more difficult to destroy such a focus completely by surgery. That is why PARKER and JACKSON advise the irradiation, at any rate, of surgically treated cases. Altogether 15 of their cases of paragranuloma showed remissions of more than 5 years. But also in their group of Hodgkin's granuloma there is one case — at least no more are mentioned — with remissions of 12 and 9 years (still continuing).

Long remissions occur in the communication of MEDINGER and CRAVER, who, if possible combine intensive local irradiation with supplementary total irradiation. So this method is in fact a variation of GILBERT's one. In their group of 94 unselected cases there are found 7 who have been free from symptoms for more than 5 years.

Of special interest are the results of SLAUGHTER and CRAVER. In their group of 265 cases there are 6 who are living and more than 5 years free from symptoms. The general mode of treatment was palliative with moderate doses, enough to obtain remissions, but CRAVER himself remarked that these best results were obtained when an attempt was made to destroy definitely a single observable focus. This was in accordance with the conception of FINZI. At the 5th International Radiological Congress in 1937 FINZI explained that he treated simple cases with intensive local irradiation and obtained results of 18 years freedom from symptoms. SLAUGHTER and CRAVER also quote the report of BAKER and MANN about 2 cases, treated by local excision of the focus in the neck with consecutive clinical health during 10 and 12 years respectively. However, they think it dangerous to speak of a cure, as in their own series there are another 3 cases, which showed remissions of 10, 11 and 16 years respectively, but yet afterwards developed a relapse.

O'BRIEN also described a remission of 19 years after surgical excision of cervical nodes in 1920. In 1939 again cervical nodes appeared, accompanied by a mediastinal tumour. The nodes were excised again and the mediastinal tumour disappeared after deep roentgen-therapy.

Finally, I would mention one case out of a series of 60, described in the book of RATKÒCZY, who was treated with heavy dosage and remained alive and free from symptoms for 5.5 years.

Author's own Cases

The group of 32 patients, who are treated in our department and of which the histo-pathological diagnosis could be made, is far too small to be of any statistical value. When possible, the patients were treated by rather intensive local irradiation (200 K.V., 6 mA, 0.5 mm Cu), while also regions, where non-observable foci were suspected, were irradiated in a number of cases. Owing to various circumstances, advanced and rapid forms, war-circumstances etc. 10 patients could not be treated in such a way that one could speak of a complete treatment. They are all dead. Of the remaining 22 another 12 died, among which was one, who survived 12 years. Among the 10 left, who are alive up to now, there are 6, who have passed the 5-years survival-time. So 22 % of the whole group survived more than 5 years. Within the scope of this article, however, it is most interesting, that there are 2 cases who

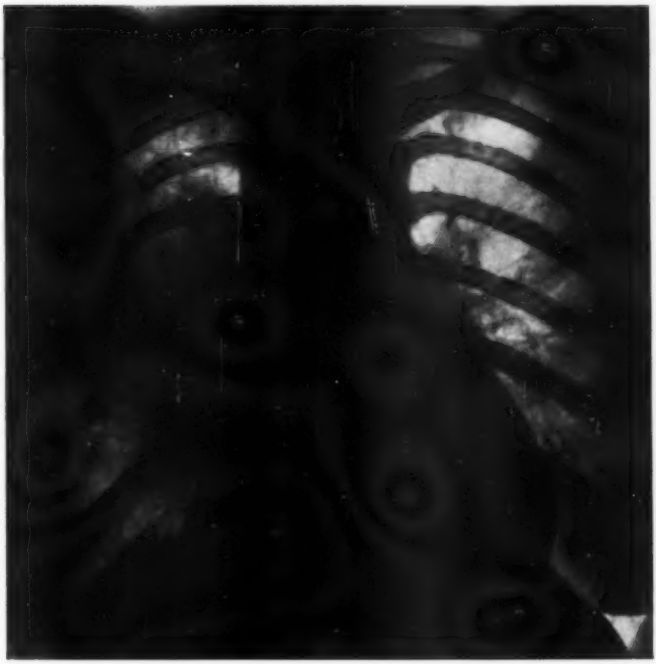

Fig. 1.

remained free from symptoms during more than 5 years after their last treatment.

1. Patient B., a woman, 22 years old, came in April 1939 for treatment. On the right and left side of the neck there were palpable and painless glands, an exploratory excision of which revealed the histo-pathological picture of Hodgkin's disease. The spleen was not palpable nor were there any other palpable glands. The roentgen examination of the chest, however, showed an enlargement of the upper mediastinum and an atelectasis of the right middle-lobe (Fig. 1). During 14 days of the month of April 1939, the different foci were irradiated, the neck-glands at first with the moderate dosage of 4 × 150 r (measured in air), the mediastinum from 4 directions with 3 × 200 r on each field. After 6 weeks of rest the nodes in the neck had disappeared and the deviations in the chest had decreased considerably. In July 1939 it was tried to destroy the remnants and the mediastinum was irradiated again from 4 directions, each field receiving again 3 × 300 r. In December 1939 a series of irradiations of the para-aortal glands of the upper abdomen from 2 directions (3 × 300 r on each field) were applied for safety. In August 1940 the irradiation of the neck appeared to have been insufficient and the neck was again irradiated from both sides (a total of 850 r on each field). Hereafter a complete remission occurred, which, in fact, continues up to now. At a check in June 1943 no glands or other signs of the disease could be ascertained. But both hili appeared a little too heavy

Fig. 2.

and as we were not sure whether this was a consequence of cicatrization, it was considered a safe measure to add a new series of irradiations. These, in fact prophylactic irradiations, took place in July and September 1943. The mediastinum was irradiated again from 2 directions (4 × 300 r on each field) and the para-aortal glands of the upper abdomen received from 3 directions 4 × 300 r on each field.

Since the 11th of October 1943 our patient has not received any more treatment and is now, nearly 6 years after the last treatment, free from symptoms. In 1945 she married and since gave birth to two healthy children. She is now expecting her third child and is in a splendid condition. The roentgen examination of the chest showed accentuated markings, especially of the right lung and apparently due to fibrosis after the heavy irradiation (Fig. 2). The mediastinum posterior was clear. The sedimentation rate was 15—37 which could not be considered very high as the patient was pregnant. The blood-picture showed some leucocytosis with a slight relative lymphopenia (Er. 3,610,000, Leuc. 10,000: Eo. $2^1/_2$, Rods 3, Segm. 73, Lymph. 14 and Mon. $7^1/_2$ %).

2. The second patient was a girl 15 years of age, who was sent for treatment in March 1944. She had observed some small painless glands at the left side of the neck and had not felt very well for some time. The microscopic examination of an extirpated gland gave the diagnosis: Hodgkin's disease. The roentgen examination of the chest revealed a big round tumour in the upper mediastinum (Fig. 3). The tumour in the mediastinum

Fig. 3.

was thereafter irradiated from 3 directions with a dosage of 6 × 200 r (air) on each field, while the region of the extirpated glands received additional irradiation of 4 × 200 r. Within 2 months all deviations disappeared. Since the last irradiation on 12.4.1944 no more treatment has taken place and, up to now, $5^1/_2$ years after the last irradiation the patient has remained completely free from symptoms. In March 1949 the roentgen picture of the chest was quite normal (Fig. 4). There were no glands palpable. Even the sedimentation rate was normal (4—12) and so was the blood-picture (Er. 4,280,000, Leuc. 8,200: Eo. 2, Segm. 37, Lymph. 33, Mon. 8).

What conclusions can be drawn from these cases?

1. As with most cases extracted from the literature, one sees that the long remission of the first patient was obtained by intensive penetrating irradiation and that of the second patient by a somewhat more moderate dosage, apparently due to extreme radiosensitivity.

2. The case-record of the first patient makes it clear, in accordance with GILBERT, that pregnancy is of no influence on the disease. The reason that we must not advise patients to marry is, however, that only

Fig. 4.

a very small number of patients enjoy the privilege of obtaining such long remissions as described.

3. In contradiction with what is sometimes said, that during the remissions the blood-picture and the sedimentation rate remain pathological, the second patient shows both of them quite normal. This was also found with a third patient, who was sent for treatment in July 1946 and after treatment has since been free from symptoms. When coming for a check in December 1948 she was also pregnant and even under this circumstance had a sedimentation rate of 2—4.

4. In accordance with what SLAUGHTER and CRAVER noticed, considering the etiology, one can say that Hodgkins disease is certainly not a primary and general systemic disease. One has to admit that the disease starts locally and then spreads metastatically.

5. The question has to be put whether the additional total irradiation, as used by MEDINGER and CRAVER, may lead to a greater number of long remissions. If this would be so, one can also try to complete the

local treatment by a few additional treatments with nitrogen-mustard, in order to destroy the small non-observable metastases. The author has tried this with a few patients but, up to now, with no result. One patient, sent for treatment with glands in the right axilla only, was irradiated locally and received during the following months two treatments with nitrogen-mustard (bis), each consisting of 4 injections of 10 mg per kg weight. He died in July 1949, after having suffered from general malaise during the last months, but without any signs of localized disease. The obduction revealed very small foci in most organs, but no big masses. The second patient, admitted for treatment also in March 1948, after extirpation of some glands in the region of the appendix, received the same kind of treatment. He is still alive and there are no glands palpable, but he developed an aplastic anaemia with a very bad prognosis. So these two cases do not yield any encouragement that this method may give better results.

Note. Immediately after the writing of this study the case history of the first of the author's patients has tragically stopped. Having given birth to her third child (at home) in the middle of September and having disregarded some pain in the left leg for some days, she left her child-bed for the first time on the 20th of September. After a quarter of an hour she suddenly felt ill and died within a few minutes, apparently from embolism.

SUMMARY

The author considers a number of long remissions in Hodgkin's disease which are found in the literature and describes two of his own cases of continuing remissions of nearly 6 and $5^1/_2$ years respectively. It appears that all long remissions, as far as communicated, have been obtained by complete extirpation of the glands in very early cases or by the application of intensive penetrating irradiation, both measures aiming at the destruction of the observed and suspected foci.

ZUSAMMENFASSUNG

Der Verfasser gibt eine Übersicht über eine Anzahl in der Literatur beschriebenen Fälle langer Remissionen bei Hodgkin'scher Krankheit und fügt zwei eigene Fälle hinzu. Es ergibt sich, dass diese langen Remissionen erreicht wurden mittels Anwendung radikaler Exstirpation in sehr frühen Fällen oder mittels intensiver und tiefer Röntgenbestrahlung, Massnahmen die auf eine völlige Vernichtung der observierten oder vermuteten Herde zielen.

RÉSUMÉ

Aprés avoir passé en revue un certain nombre de cas de longues rémissions de la maladie de Hodgkin, communiqués dans la littérature, l'auteur rapporte deux propres cas avec des rémissions d'environ 6 et $5^1/_2$ ans. Il paraît que toutes les longues rémissions ont été obtenues soit par l'excision complète des foyers dans les cas très précoces, soit par une irradiation intensive et pénétrante, les deux traitements visant à la destruction complète des foyers observés et soupçonnés.

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RADIOLOGISCH INSTITUUT AKADEMISCH ZIEKENHUIS, GRONINGEN, HOLLAND.

HEREDITARY CONGENITAL ABNORMALITIES OF THE ELBOWS, KNEES AND NAILS IN FIVE GENERATIONS[1]

by

L. S. Wildervanck, Groningen

The family examined consists of 53 members, 22 of them show — in various combinations — abnormalities, mentioned in the title. They are: luxation of the capitulum radii, luxation or absence, resp. hypoplasia of the patella, dystrophy or absence of nails, and some other anomalies, *e. g.* exostoses. 8 persons are deceased (†), about them I got information through relatives, those marked with ** are examined by myself, those marked with * are examined by a colleague. Many skiagraphs were made, most of them in the Roentgenological Institute of the State University of Groningen (Professor Dr. S. KEIJSER).

In the pedigree »E» means anomaly of the elbow(s), »K» anomaly of the knee(s), »N» anomaly of the nails, »F» crooked little finger(s), »T» stiff big toes, ? not known, ( ) examined but anomaly dubious. For the deceased persons I refer to the pedigree, of the other members of the family I will give a short description.

III Generation.

No. 11. *Elbows:* right: radius luxated forwards to a high degree (fig. 1). Left: radius luxated backwards (figs. 2 and 3). On both sides an exostosis of the ulna (fig. 3). Both capitula rounded, the colla narrowed. *Knees:* both patellae luxated totally to lateral (not movable), hypoplastic. *Nails:* the thumbs have no nails at all, the others are normally developed. Nearly all the nails have large, triangular lunulae (see *e. g.* fig. 17, prob. no. 12).

[1] Submitted for publication, Aug. 27, 1949.

Fig. 1. Fig. 2. Fig. 3.

Fig. 1. Prob. 11. Right elbow. Capitulum radii luxated forwards and rounded.
Fig. 2. Prob. 11. Left elbow. Capitulum radii rounded and luxated backwards. Exostosis of the ulna.
Fig. 3. Prob. 11. Left elbow. Backward luxation of the radius.

No. 12. *Elbows:* both capitula radii conspicuously prominent, luxated backwards (for the left see figs. 4 and 5), capitula rounded, colla as no. 11, the proc. coronarius of the ulna has a pointed exostosis as with no. 11. Capitula humeri insufficiently developed. Both little fingers are congenitally crooked. *Knees:* on both sides the kneecaps are smaller than normal (for the left see fig. 10 on which two outlines are marked of normal patellae after skiagraphs from the archive of the Roentgenological Institute). Tuberositates tibiae left and right very prominent. *Nails:* of both thumbs, the part turned towards the fingers is dystrophical (fig. 17).

No. 13. *Elbows:* backward luxation of both capitula radii. Right little finger crooked. *Knees:* both patellae luxated to lateral. The condyli mediales of both femora are highly developed and give the knees a deformed appearance. Both big toes are stiff in all the joints. *Nails:* only the nail of the left little finger is normal, those of the thumbs are totally absent, those of the other fingers are little developed and have lengthwise furrows and gaps (fig. 18).

IV Generation.

No. 19. Right *knee* shows an habitual luxation of the patella. *Nails:* of both thumbs the nails are absent.

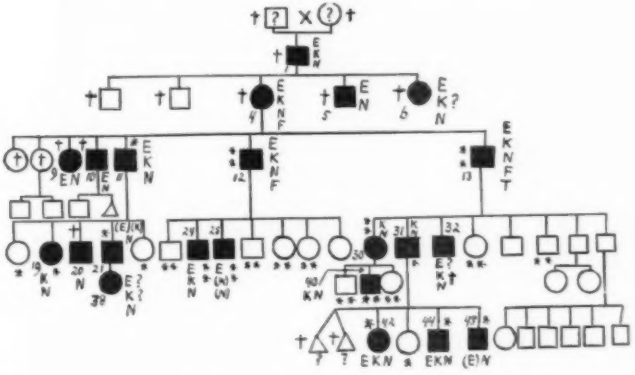
Fig. 4.

Fig. 5.

Fig. 6.

Fig. 4. Prob. 12. Left elbow. Exostosis of the ulna.
Fig. 5. Prob. 12. Left elbow. Backward luxation of the radius, capitulum rounded.
Fig. 6. Prob. 24. Left elbow. Capitulum radii rounded, capitulum humeri insufficiently developed.

No. 21. *Knees:* patellae smaller than normal. *Nails:* the thumbs have no nails at all, the others are split and atrophical.



No. 24. *Elbows:* capitula radii in the normal place but rounded (left, see fig. 6). Capitula humeri insufficiently developed. Exostosis on the proc. coronarius ulnae. *Patellae* somewhat hypoplastic. On the right a patella with 3 little bone nuclei beside the true patella (fig. 11).

No. 25. *Elbows:* right: capitulum radii prominent to a high degree, left similar, but not to such a high degree. Right and left luxation back-

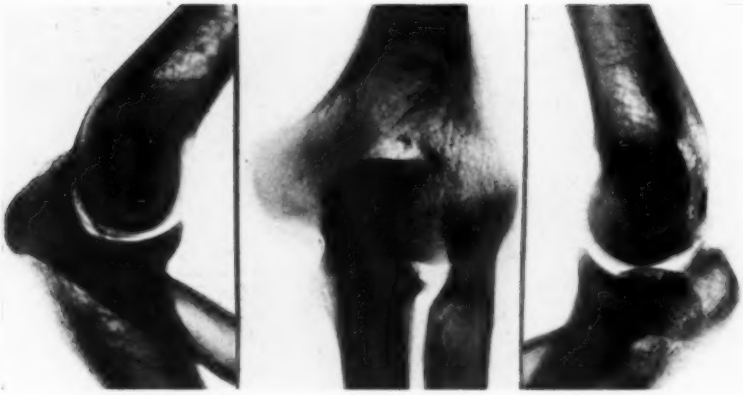


Fig. 7. Fig. 8. Fig. 9.

Fig. 7. Prob. 25. Right elbow. Capitulum radii rounded and backwards luxated. Capitulum humeri insufficiently developed.
Fig. 8. Prob. 25. Right elbow. Backward luxation of the radius.
Fig. 9. Prob. 25. Left elbow. Backward luxation of the (rounded) capitulum radii.

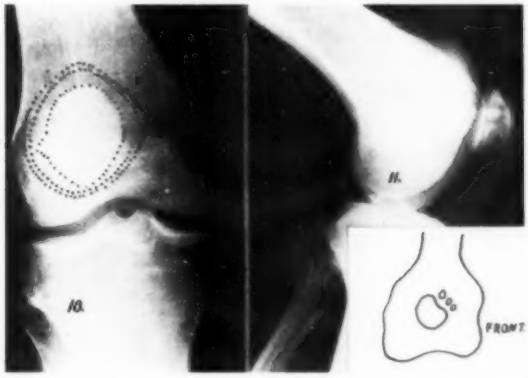


Fig. 10. Fig. 11.

Fig. 10. Prob. 12. Left knee. Hypoplasia of the patella.
Fig. 11. Prob. 24. Patella with three little bone nuclei beside the true kneecap.

ward. Capitula rounded (right: figs. 7 and 8, left: fig. 9). *Patellae* somewhat small.

No. 30. *Knees:* patellae on both sides luxated to lateral (right: fig. 12). *Nails:* on the thumbs the nails are absent (fig. 19 A), the other nails show clefts.

Fig. 12.

Fig. 13.

Fig. 12. Prob. 30. Right knee. Patella luxated to lateral.
Fig. 13. Prob. 31. Right elbow. A well formed joint.

No. 31. *Elbows:* no abnormalities. A skiagraph (right: fig. 13) shows a well formed capitulum radii with a caved surface and a normal broad collum. The capitulum humeri is also well developed. *Knees:* patellae totally luxated to lateral and too small. Tuberositates tibiae are abnormally large. *Nails:* on the lateral sides of the thumb-nails only little indurations, on the indices only on the thumbside some development of nail.

No. 38. *Nails* partially absent.

No. 40. (8 years old.) The *kneecaps* are absent on both sides (right: fig. 14). *Nails:* on the thumbs no development of nail (fig. 19 B), on the indices small pieces of nail.

No. 42. 8 years old. On the skiagraphs, notwithstanding the incomplete forming of bone tissue, a luxation of the *radius* backward-lateral is to be seen (left: fig. 15). *Knees:* patellae abnormally small and frayed for his age (right: fig. 16). *Nails:* as the father, no. 31.

No. 44. As no. 42.

No. 45. *Elbows* as no. 42, *knees* normal.

We see that the abnormalities occur in varying degrees, neither are they all of the same nature. That the elbow joint must be considered in its entirety and not only the capitulum radii is clear from the frequent

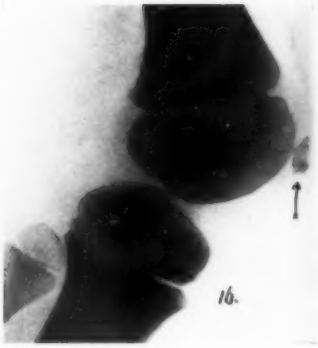


Fig. 14. Fig. 15. Fig. 16.

Fig. 14. Prob. 40. Right knee. Absence of patella.
Fig. 15. Prob. 42. Left elbow. Luxation of the radius backward-lateral.
Fig. 16. Prob. 42. Right knee. Patella abnormally small.

underdevelopment of the capitulum humeri. The epicondylus humeri is sometimes very strongly developed (prob. no. 13), the ulna has often a pointed exostosis towards the radius. With the luxated forms a good circumferentia articuli radii moving in the incisura radii ulnae is practically out of the question. The same holds good with the knee joint: the patella may be absent or underdeveloped or/and luxated, it also often occurs that the tuberositates tibiae are more than normally developed, so with the condyli femoris. There is sometimes a conspicuous valgus position.

It is worth while to investigate in how far the patients are hampered by their abnormalities: in short we can say that in the elbow joint the pro- and supination is often very limited, the extension is in most cases only possible to about 160 degrees. The persons with luxated kneecaps often fall backwards, it is difficult to descend the stairs. The boy with absent patellae, on the contrary, could leap a ditch!

In the literature we find a great many publications dealing with hereditary luxation of the radius, absence of the patellae or luxation of them, dystrophy or absence of the nails. A combination of two of those abnormalities is not so often found. On the entire triad wrote WREDE (1), FIRTH (2) and LESTER (3), TRAUNER and RIEGER (4), OREL (5), ÖSTERREICHER (6), TURNER (7), MONTANT and EGGERMANN (8), SEVER (9) and

Fig. 17.

Fig. 18.

Fig. 19.

Fig. 17. Prob. 12. Nails of both thumbs partially dystrophical.
Fig. 18. Prob. 13. Dystrophy of the nails.
Fig. 19 a. Prob. 30. Nails of the thumbs absent.
Fig. 19 b. Prob. 40. The thumbs have no nails.

SENTURIA and SENTURIA (10). The number of examined members in their families, however, is in most of the publications small.

It is clear from our pedigree that the hereditary transmission of the complex of anomalies — whether complete or not — is not sex-linked and is irregularly dominant, though not to such a degree that generations are passed over in which none of the three anomalies occurs, but in the sense that the abnormalities appear in a greater or lesser degree: the expressivity is very unequal. The assumption of 3 incompletely linked geneses for elbows, knees and nails, would in my opinion seem the most plausible explanation.[1]

[1] A genetical analysis and a detailed discussion of the literature will be published in *Genetica*.

SUMMARY

Examination of a family of 53 members, 22 of whom show anomalies in different combinations of the *elbows* (luxation, subluxation, or malformation of the capitulum radii, insufficient development of the capitulum humeri, exostoses of the ulna), of the *knees* (luxation, absence or hypoplasia of the patella) and of the *nails* (absence or dystrophy). The degree of anomalies differs widely, they are irregularly dominant and are probably caused by three incompletely linked genes.

ZUSAMMENFASSUNG

Es wurde eine Familie von 53 Mitgliedern untersucht von denen 22 Abnormalitäten in verschiedenen Kombinationen aufwiesen an den *Ellbogen* (Luxation, Subluxation oder Veränderung des Capitulum radii, unvollständige Entwicklung des Capitulum humeri, Exostosen der Ulna), an den *Knien* (Luxation, Fehlen oder Hypoplasie der Kniescheibe) und an den *Nägeln* (Fehlen oder Dystrophie). Der Grad der Veränderungen war sehr verschieden, die Anomalien sind unregelmässig dominant und werden vermutlich durch drei unvollständig gekoppelte Gene verursacht.

RÉSUMÉ

Examen d'une famille comprenant 53 membres parmi lesquels 22 présentaient différentes combinaisons d'anomalies du *coude* (luxation, subluxation ou malformation du capitulum radii, développement insuffisient du capitulum humeri, exostoses du cubitus), du *genou* (luxation, absence ou hypoplasie de la rotule) et des *ongles* (absence ou dystrophie). Le degré des anomalies est très différent, elles sont irrégulièrement dominantes, et sont probablement causées par trois gene incomplètement couplées.

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(CHIEF: ROLF BULL ENGELSTAD, M. D.)

ATTEMPTS AT GASTRIC EXAMINATION BY PHOTOFLUORGRAPHIC METHODS[1]

by

Rolf Bull Engelstad and *Selmer Rennæs.*

In the organized control of cancer, the early detection of carcinoma of the stomach appears as one of the central problems. However, very little progress has been made in this particular field. Any effort, clinical or roentgenologic, to improve these conditions, seems justified, therefore. Even if one may expect by anticipation that no single metod will be effective, one may think that a combination of diagnostic procedure may be developed, whereby large segments of the general population may be examined, and together make it possible to diagnose more gastric carcinoma at an earlier stage as hitherto.

As an effort in this direction we have carried out some experiments in the field of gastric photofluorgraphy. The experiments were started in January 1949 at the Norwegian Radiumhospital, Oslo.

In the United States as well as other countries, mass examinations hawe been carried out, entailing both roentgenoscopy (SWENSON) and roentgenography. These procedures are slow and expensive, moreover they require the prolonged services of a highly trained physician, and cannot be regarded as practical in the examination of large population groups.

The first attempts in the field of gastric photofluorgraphy was laid down by SWENSON. In Finland, WEGELIUS and NOSCHI in 1948 constructed a small photofluorgraph, a so-called *Wegnograph*, intended for detail photofluorgraphy.

The principal disadvantage of the various methods of gastric photofluorgraphy has been that undesirably large doses of radiation must be used, because of the relative inefficiency of the photofluorgraphic

[1] Read at the Meeting of the Northern Association for Medical Radiology, June 10—12, 1949; submitted for publication, Oct. 24, 1949.

cameras commonly in use. A considerable improvement was therefore the SCHMIDT camera, in wich the principal lenticular element consists of a large spherical mirror, by virtue of which the f/number rating has been increased from f/1.5 to f/0.8 and more. The Schmidt camera was introduced in photofluorgraphy by the Danish engineer C. H. HELM and the physician H. CHRISTENSEN in 1939. However, its general use was not adopted until after the World War II.

In 1948 SWENSON in a publication stated that he intended to adapt his photoroentgenograph according to the Schmidt principle. In a personal communication in 1949 he told that the installation was accomplished and that mass examinations were being carried out at three centra in the United States. While our investigations were still in progress, a publication was issued from Johns Hopkins Hospital (ROACH, SLOAN and MORGAN) concerning experience gained from some preliminary experiments. So far, however, no publications have appeared concerning the results of mass examination by this method.

Personal Examinations

The equipment employed in our experiments was a conventional pulmonary photofluorgraph with Schmidt optics using 70 mm perforated film. In mass examinations the Schmidt optics using 70 mm perforated film (Fig. 1) is of essential importance. With the increased speed provided by the Schmidt camera it is possible to take photofluorgraphic films of the abdomen with the expenditure of the same energy as that used in conventional roentgenography. This on the average corresponds to a roentgen dosage at the skin surface of approximately 0.5 r, while the skin dosage in photofluorgraphy without the use of Schmidt optics will have to be increased to about 9 or 12 r for satisfactory photofluorgrams to be obtained (HODGES). A dose of this order cannot be considered as harmless when several exposures are made, or in the case of repeated examinations.

Position

The patients were mainly examined in the erect posture. Exposure times ranging from 0.8 to 2 seconds at a tube ratings of 30 mA and 85 kV were used, and 3 films were taken, viz., 1 in the antero-posterior position, 1 in the antero-oblique and 1 in the oblique position with the screen being adjusted merely in relation to the iliac crest, without previous screening.

Photofluorgraphic films were also taken with the patient in the prone position, the photofluorgraphic camera being mounted below a conventional horizontal roentgenographic table, and the tube from a

trochoscope being used. The tube ratings varied from 75 to 80 kV at 200 mA and exposure time from 0.15 to 0.30 seconds. A tube screen distance of 90 cm was used. So far we have not been able to determine which position is the most suitable for mass examination. The determining factor regarding this problem depends on in which position the most satisfactory results are obtained. Examination of the patient in the prone position supplies the best means of adequate compression and gives the most satisfactory visualization of the cardiac region. In mass examination, however, examination of the patient in the erect posture is obviously far more convenient.

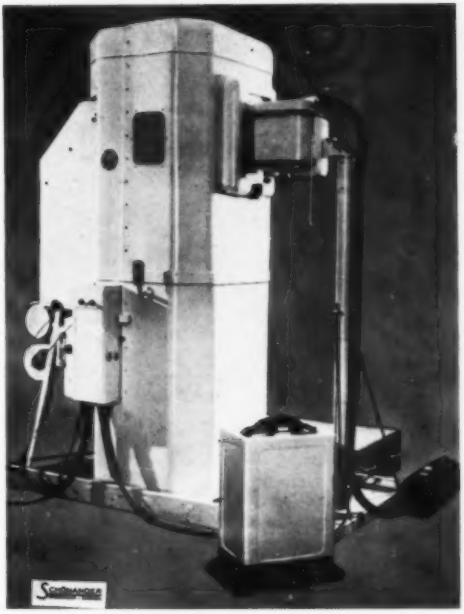

Fig. 1. Mass roentgenography unit (SCHÖNANDER) with full protection for the operator. Camera with mirror optic.

The amount of contrast medium used has varied somewhat in these preliminary experiments. First we gave two swallows (approx. $^1/_{24}$ l) of barium-contrast for the first exposure, and up to one glass (approx. $^1/_6$ l) for the following exposures. The erect posture requires the use of larger amounts than does the prone position. When merely a small amount of contrast medium is ingested, it takes a comparatively long time before adequate filling as far down as the pyloric region is accomplished. Without screening and without massage of the stomach the use of a small amount caused a considerable delay in the examination. We have consequently adopted the use of larger amounts viz. $^2/_3$ glass (approx. $^1/_8$ l) of contrast medium immediately before the first film is taken and have thus got adequate filling of the stomach including the duodenal bulb and the upper portion of the duodenum even on the first film.

Time of Exposure

Films were made immediately after the ingestion of the contrast medium, and up to fifteen minutes after the ingestion. As a mean we have adopted exposure four to five minutes after the ingestion of the

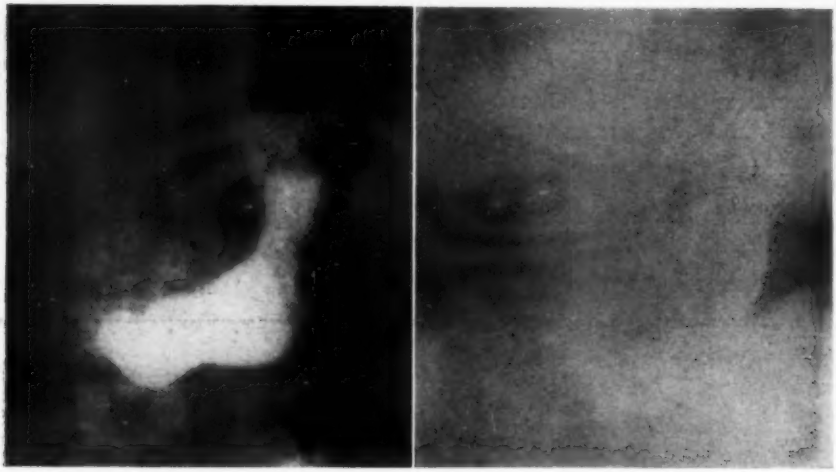

Fig. 2 a. Fid. 2 b.

Fig. 2 a and Fig. 2 b. Photofluorgraphic films taken with and without the use of Schmidt optics with the same exposure at the same tube potential and tube-screen distance. The difference is striking.

contrast medium. At this juncture the contrast will be evenly distributed as far down as the duodenum.

The experiments so far include 150 individuals above the age of 40 years, without symptoms referable to the gastrointestinal tract. In no instance gastric carcinoma was detected, nor recent peptic ulcers, though lesions after previous ulcers were revealed in some subjects. However, the presence of a gastric cancer in such a small series can hardly be expected.

In order to test the diagnostic value of the photofluorgraphic method we have so far examined 8 patients with roentgenographic evidence of cancerous infiltration of the stomach.

One of these patients exhibited major changes in the cardial region with infiltration of the proximal portion of the stomach. The roentgenogram and the corresponding photofluorgraphic film are shown in Fig. 3 a and Fig. 3 b, respectively. This patient was examined in the prone position after ingestion of $^2/_3$ glass (approx. $^1/_8$ l) of contrast medium. Three films were taken, and on all films the infiltration is clearly revealed.

Another patient exhibited infiltration involving the entire corpus of the stomach. The roentgenogram and the fluorgraphic film are shown in Fig. 4 a and Fig. 4 b, respectively.

Fig. 3 a.

Fig. 3 b.

Fig. 3 a and Fig. 3 b. Roentgenogram and photofluorgram of a case of cancer of the cardia.

Regarding minor changes we examined a third patient, who exhibited a prepyloric constriction associated with retention (periodically positive benzidine reaction in the stools). The roentgenogram and the photofluorgraphic film are shown in Fig. 5 a and Fig. 5 b, respectively. However, the patient resisted operation, and the true nature of the lesion was consequently not revealed. In the form it appears on the photofluorgraphic film this suffices for making a diagnosis of prepyloric constriction.

Comments

With a photofluorgraphic equipment supplied with merely a 30 mA roentgen tube we have succeeded in taking adequate photofluorgraphic films of up to 30 individuals per hour (90 exposures). Roentgenographic evidence of gastric lesions in 8 patients were revealed similarly clearly on photofluorgraphic films.

In conventional roentgenographic examination much stress is commonly placed on screening, palpatory findings, and adequate positioning. The photofluorgraphic methods breaks with conventional principles. However, by this method too, three or more films can be taken in different positions and if necessary with different amounts of contrast medium being used. In most instances, such a series of films yields certain information as to whether the contour is soft and elastic. Control roentgenograms, however, were necessary in several instances in our

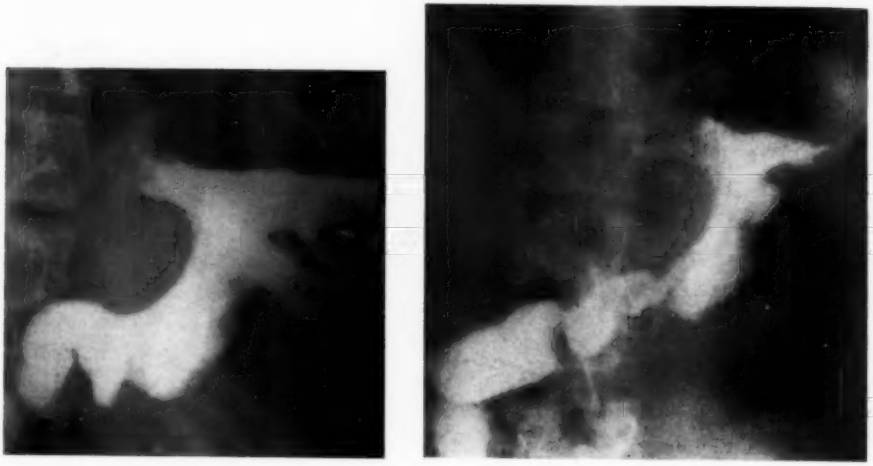

Fig. 4 a. Fig. 4 b.

Fig. 4 a and Fig. 4 b. Extensive infiltration of the corpus of the stomach as revealed on the roentgenographic and photofluorgraphic films, respectively.

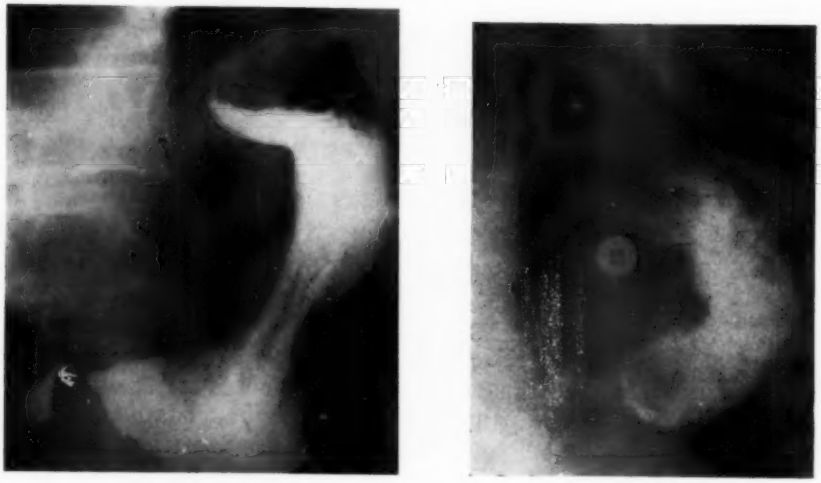

Fig. 5 a. Fig. 5 b.

Fig. 5 a and Fig. 5 b. Roentgenograms and photofluorgrams of a prepyloric constriction. The last shows the retention of the food.

experiments, particularly in the case of abnormal shape and position of the stomach.

The advantages of the photofluorgraphic process are that it can be quickly performed. Thus, more than 30 individuals can be examined per hour if not more than three films per patient are made. Also, the initial cost of the film is very small, merely 30 øre per film, *i. e.* about 1 krone (approx. 15 cents) per three exposures. The operating of the unit is quite simple and does not require the services of a highly trained physician. If provided with a photo-electric cell, the unit can actually be operated by anyone.

Conclusions, Program

The intention of this preliminary report is merely to give an account of our technique used for photofluorgraphy in examination of the stomach. And to show that the method, as used in mass examination with the performance of up to 30 examinations per hour (90 exposures per hour), gives results which so far seem highly encouraging.

Other conclusions cannot be drawn from these preliminary experiments. However, based upon these preliminary results, we intend to pursue our studies and extend our experiments to a larger number of cases so that the reliability of the method can be determined on a statistical basis as far as such is feasible.

We do not presume that photofluorgraphy will proove completely reliable for early detection of carcinoma of the stomach in mass examination. However, we consider an effort to determine *the exact degree of reliability* of the method as highly justified. We are fully aware of the defects of the photofluorgraphic method and that it represents merely a means of rough examination, and that additional procedures, clinical and roentgenographic, will be necessary.

The problem is simply a question whether the use of photofluorgraphy may contribute so much to the detection of silent, or at least undetected and operable cases of gastric cancer that its use may be justified — possibly combined with other methods of mass examination — in examination of large segments of the population.

For practical reasons this preliminary study, which ought to include several thousands of individuals has been limited to them above the age of 40 years.

SUMMARY

Photofluorgraphic equipment and technique as employed at the Norwegian Radium Hospital are described. The patients have mainly been examined in the erect posture by means of a transportable unit equipped with Schmidt camera (85 kV, 30 mA, 0.8—2.0 seconds, 70 mm perforated film), which is able to accomodate 30 examinations per hour if not more than three films per patient are made. In photofluorograms of 150 individuals without stomach trouble cancer was not detected. In 8 patients in whom roentgenographic changes had been demonstrated previously, the photofluorgraphic films revealed the same changes just as clearly as did roentgenograms.

ZUSAMMENFASSUNG

Aussteuer und Technik bei Schirmbilduntersuchung des Magens am Norwegischen Radiumhospital sind beschrieben worden. Die Patienten sind hauptsächlich in stehender Stellung untersucht worden, mittels einem tragbaren Apparat mit Schmidt Kamera, (85 kV, 30 mA, 0.8—2.0 Sek., 70 mm Film), bei welchem 30 Untersuchungen pro Stunde sich durchführen lassen, wenn nur 3 Exponierungen pro Person gemacht sind. An Schirmbildern von 150 Personen ohne Magensymptomen wurde keiner Fall von Karzinom entdeckt. In 8 Personen mit früheren erkannten röntgenologischen Veränderungen des Magens zeigten die Schirmbilder dieselbe Veränderungen ebenso deutlich.

RÉSUMÉ

Description de l'équipement et de la technique radiophotographiques pour l'estomac en usage à l'Hôpital Norvégien du Radium. Les photographies ont été prises surtout en position debout avec un appareil transportable muni de la chambre noire de Schmidt (85 K.V., 30 mA, 0.8—2.0 secondes, films de 70 × 70 mm). On peut examiner en série 30 personnes par heure (90 poses). Les radiophotographies de 150 sujets sans symptomes gastriques n'ont révélé aucun cas de cancer de l'estomac. Des altérations radiologiques de cet organe constatées auparavant dans 8 cas apparaissaient.

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DIFFERENTIATION AND IRRADIATION[1]

by

S. Ry Andersen

During the half century that roentgen rays and radium have been used in the treatment of cancer, the question has been raised repeatedly as to whether these rays possess a power to induce increased differentiation in malignant tumours and whether their curative effect might be partly or wholly due to increased differentiation. In my thesis for the doctorate (1949) I reported studies of this problem on a broad basis. The reader is referred to the bibliography in this book, and only a few of the earlier investigations will be mentioned here.

In this paper, the term differentiation is used to designate transformation from a more unripe to a more ripe, specialized state. An outstanding feature of malignancy — although it is not demonstrable in all cases — is a more or less diminished or abnormal differentiation. It is so characteristic that it constitutes one of the most important clues in deciding histologically, whether a specimen is cancer or not. Similarly, the absence of differentiation is often an important criterion of the major or minor malignancy of a growth. The best grading of malignant tumours is the one made by BRODERS (1920), and his system now comprises 4 grades (1940). BRODERS is of the opinion that the grade of differentiation of a malignant tumour is a fit expression of the degree of malignancy, the most highly differentiated tumours being considered least malignant. In my opinion, however, the degree of differentiation is merely one of the properties — an extremely important one it is true — deciding the malignancy of a tumour.

Previous investigations into morphological cellular changes in malignant tumours following therapeutic irradiation have afforded conflicting results concerning differentiation.

PERTHES (1903) and APOLANT (1904) advanced the view that histologically demonstrable radiation changes in malignant tumours should

[1] Submitted for publication, Nov. 16, 1949.

be interpreted as a sign of degeneration, and these observations have been supported by numerous workers, *e. g.* MELNICK and BACHEM (1937), ENGLMANN (1938), and LACASSAGNE and GRICOUROFF (1941). The theory of differentiation is not directly mentioned by these workers, however.

In 1907 DOMINICI and BARCAT suggested that the main effect of the radiation should be due to increased differentiation (ripening) of the tumour cells. Since a fully differentiated cell cannot divide and thereby give rise to new neoplastic growth, it must, according to the theory, degenerate and die, partly because of degenerative injury caused by the radiation. The theory of differentiation has received support from many workers, *e. g.* CLUNET (1910), LAHM (1927, 1928), and DUSTIN (1927—1930). Recently, it has been supported by American workers, FRIEDMAN (1939, 1940) and WARREN (1944), and in major English works (1941—1946) by GLÜCKSMANN, SPEAR, KOLLER, SMITHERS, and DONALDSON.

Doubts as to the correctness of the theory have, however, been advanced by *inter alia* LUBARSCH and WÄTJEN (1928), STEWART and FARROW (1940), and, in 1946, by KOLLER and SMITHERS. These critics emphasize, among other things, that the increased differentiation may be merely relative as a result of tumour breakdown.

The vast majority of the workers base the theory of differentiation on cornification in squamous-cell carcinoma. GLÜCKSMANN and his associates use a quantitative histological analysis, worked out by GLÜCKSMANN, and stress the importance of the increase in size of the tumour cells, the staining reactions with Heidenhain's azan, and the cornification, whereas epithelial pearls and parakeratosis are not counted.

My Investigations

I examined a number of characteristic types of tumours which, theoretically, should have a possibility of exhibiting histologically demonstrable differentiation before, during, and after radiation.

The material comprises:

(1) *Squamous-cell carcinomas:*
   (a) Squamous-cell carcinoma transplanted into mice.
   (b) Skin carcinoma in human beings (partly basal-cell, partly squamous-cell carcinoma).
   (c) Cervical carcinoma in human beings.

(2) *Adenocarcinomas:*
   (a) Mammary carcinoma transplanted into mice.
   (b) Mammary carcinoma in human beings.

(3) *Sarcomas:*
   (a) Spindle-cell sarcoma transplanted into mice.
   (b) Chondrosarcoma transplanted into mice.

The animal material consists of tumours transplanted into mice and treated with roentgen rays with a technique as close as possible to the fractionated roentgen-ray radiation used in human cancer. A Siemens Bomb was used, maximum voltage 193 kv., 20 ma., ½ mm. copper filter, half value layer 0.85 mm. Cu., focal-skin distance 50 cm., no applicator employed. The doses differed somewhat, but most often 400 r twice daily up to 5,000—6,000 r was used. In addition, a number of treatments were carried out in one sitting, with a dose ranging from 25 to 2,000 r.

The human tumours were submitted to the customary roentgen-ray and radium irradiation used at the Radium Centre in Copenhagen.

Histological examination was made of the animal tumours and compared with untreated tumours of the same kind. The human material comprises biopsies before, during, and after the irradiation. In all, the material comprises 986 microscopic preparations from a total of 660 tumours. The specimens were imbedded in paraffin and stained partly with hæmatoxylin-eosin and partly by the method of van Gieson-Hansen. In some cases, keratin staining was employed, partly Gram-staining and partly Heidenhain's azan staining. Often several sections were taken in various planes throughout the tumour.

All the tumours were searched for »orderly differentiation» as compared with the untreated controls.

The squamous-cell carcinomas were, in addition, searched for parakeratosis and cornification which constitute easily demonstrable signs of differentiation.

Adenocarcinomas were studied with a view to increased glandular formation.

As to sarcoma, the spindle-cell sarcoma was examined for a tendency to form collagen fibrils, and the chondrosarcoma for the amount of cartilaginous intercellular substance and for the possibility of bone formation.

Results

Among the entire material, I did not in any case find signs of increased, regular »orderly differentiation» in the radiated tumours as would be expected, if the radiation produced increased differentiation.

In the *squamous-cell carcinoma* in mice, theoretically, differentiation should be particularly easy to induce, because originally this tumour was a highly differentiated cornifying carcinoma (see Fig. 1), but during continued transplantation its differentiation was considerably reduced and arrived at a fairly constant, low degree of differentiation (see Fig. 2). A preserved capacity for further differentiation could, however, be seen from the frequent finding of traces of differentiation in the otherwise

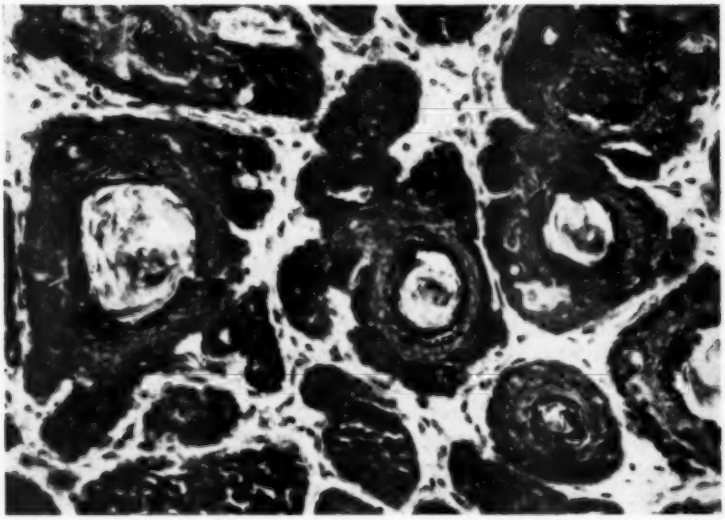

Fig. 1. Squamous-cell carcinoma Aka transplanted into mice. Spontaneous tumour. A highly differentiated cornifying squamous-cell carcinoma with numerous keratohyaline granules and large horny pearls. × 300.

undifferentiated tumour and from the even marked differentiation occurring in places in some of the controls, in the form of marked parakeratosis and cornification with parakeratotic and horny pearls (see Fig. 3).

The differentiation remained unchanged in all essentials after radiation (see Fig. 4). A few of the tumours treated with large single doses exhibited a faint increase in parakeratosis, showing no relation to the period elapsing from radiation, but no definite increase in cornification. The tumours treated with fractionated radiation failed to show any definite increase in parakeratosis or cornification as compared with the controls which, at times, exhibited quite marked differentiation, but a faint increase in both cannot be ruled out.

In my opinion, these faint and rare changes cannot be attributed with any importance as factors in tumour destruction. I do not either interpret them as a sign of differentiation, but consider the most probable explanation to be a selection of the comparatively few fairly differentiated and fairly resistant tumour cells, the undifferentiated, more radio-sensitive cells degenerating and perishing more readily. Theoretically, I had expected to find a far greater relative increase in the number of highly differentiated tumour cells than I actually did.

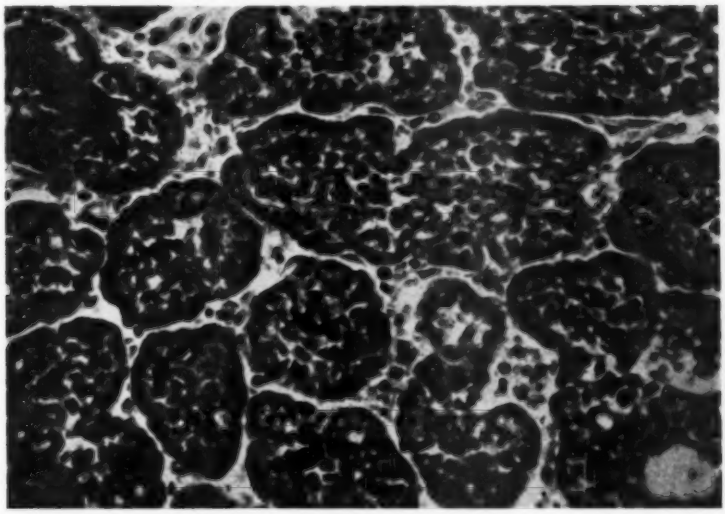

Fig. 2. Squamous-cell carcinoma Aka, 4th passage. Undifferentiated squamous-cell carcinoma showing numerous mitotic figures and moderate polymorphism.

On the other hand, the possibility cannot be ruled out entirely that the undifferentiated, radio-sensitive cells are killed by the radiation, whereas the more differentiated cells persist and go on differentiating like the cells of the normal skin, a fact which is demonstrated by the experiments with normal mouse skin.

If this explanation were tenable in the case of the tumours also, the differentiation would, however, be expected to be more diffuse and more marked, but it only involved a few, small areas in quite few tumours.

Human skin carcinoma did not exhibit signs of differentiation, not even a relative increase in the number of fairly differentiated cells.

Cervical carcinoma did not show signs of increased differentiation, and only one case revealed a marked increase in parakeratosis. In this instance, there was a pre-existing excessive parakeratosis, and the phenomenon is presumably relative too.

Adenocarcinoma, mouse as well as human mammary carcinoma, failed to show any signs of increased differentiation in the form of increased glandular imitation.

Neither did the radiated *mouse sarcomas* exhibit any signs of relative or absolute increase in differentiation, the criteria being the tendency to form collagen fibrils in the *spindle-cell sarcoma* and the tendency to form cartilaginous intercellular substance in the *chondrosarcoma.*

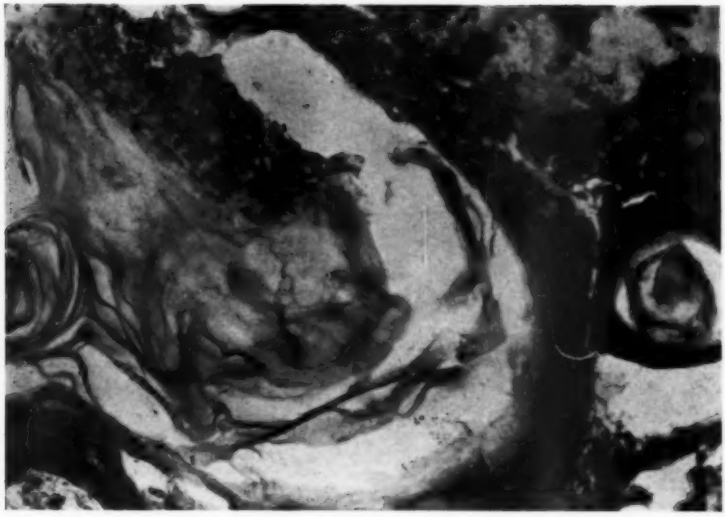

Fig. 3. Squamous-cell carcinoma Aka (No. 83), untreated control. Marked cornification with large and small horny pearls.

On the whole, the experiments speak definitely against DOMINICI and BARCAT's theory of differentiation, as studies of this extent with so varied a material and so varied a dosage of radiation must be expected to elicit differentiation, if it occurs at all.

There are numerous sources of error to account for the reports of differentiation following radiation published by so many workers, among them also experienced tumour pathologists.

The observation most commonly reported in the literature is increased parakeratosis and cornification which may easily be confused with tumour cells showing marked effects of radiation, a degenerated nucleus and an eosinophilic protoplasm (see Fig. 5).

Tumours covered by normal skin often, and particularly after radiation, show tongue-shaped masses extending down into the dermis in between the tumour cells. When the tumour as well as the epithelium show marked effects of radiation, it may be extremely difficult to decide, whether a degenerated horny pearl surrounded by granulation tissue belongs to the carcinoma or to the non-carcinomatous epidermis.

As to adenocarcinoma, errors are apt to be made in the interpretation of the frequent »pseudoacinous cavities».

In my opinion, the differentiation stated to take place in sarcoma in the form of collagen fibrils is no doubt due to misinterpretation of the

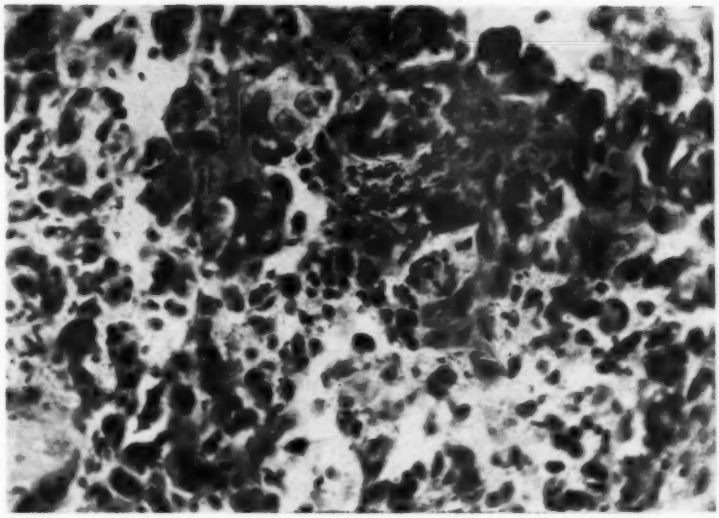

Fig. 4. Squamous-cell carcinoma Aka (No. 123). Killed 6 days after a single dose of 2,000 r. In the centre of the picture mild parakeratosis is seen. Marked effects of radiation (enlarged, polymorphous, hyperchromatic nuclei, at times multiple).

normal proliferation of fibroblasts which is a characteristic feature in radiated tumours and which later leads to the formation of collagen fibrils.

Moreover, chance plays a marked role. Most of the earlier investigations into this subject have not paid sufficient regard to the control material. One biopsy taken before the institution of treatment is of limited value, and in my opinion, studies of human tumours are applicable only when the materials are large, whereas it is not warrantable to draw conclusions from biopsies derived from one single case. My material has, in numerous instances, shown that some tumours appear to exhibit a higher (see Fig. 6), others a lower differentiation following radiation whereas an evaluation of the material as a whole reveals unaltered differentiation. This uncertainty applies particularly to mammary tumours in which the differentiation may show wide variations from one part to another in the same growth.

In studies of this particular nature, the value of spontaneous tumours is by far exceeded by that of transplanted tumours, since the latter are derived from the same tumour and since their histological architecture can be compared with numerous controls in every experiment. In such cases, the variations from one transplanted tumour to another are no

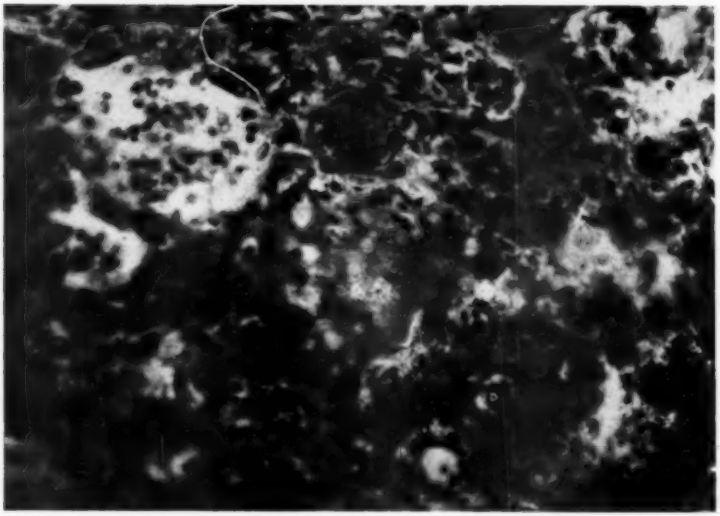

Fig. 5. Squamous-cell carcinoma Aka (No. 165). Killed after 300 r × 11 = 3,300 r. Undifferentiated squamous-cell carcinoma showing marked effects of radiation, the protoplasmic degeneration resembling parakeratosis.

greater than may sometimes be found within the same spontaneous tumour, less if anything, since tumours transplanted through several passages have a certain tendency to assume a more uniform histological appearance.

Furthermore, in transplanted tumours, the same type of tumour may be exposed to radiations with widely different dosage.

Finally, the interpretation of the histological changes is of the utmost importance. Several workers, *inter alia* GLÜCKSMANN, SPEAR, and DONALDSON interpret enlargement of the cells following radiation as a sign of differentiation. If that is so, differentiation takes place following any heavy irradiation of cells, as cellular enlargement is a constant finding after irradiation. It is not, however, in accordance with the generally accepted criteria of differentiation to interpret a ballooned, monstrous cell with a partially destroyed nucleus as a sign of differentiation, whereas the cellular changes correspond exactly to severe cell degeneration. It is true that at a certain stage of the cornification of epithelium, the cells grow larger and flatter, forming intercellular bridges, and that the nuclei degenerate, but this takes place in a regular, »orderly» way, showing increasing differentiation. Radiated tumour cells, on the other hand, are disposed in a disorderly fashion, scattered,

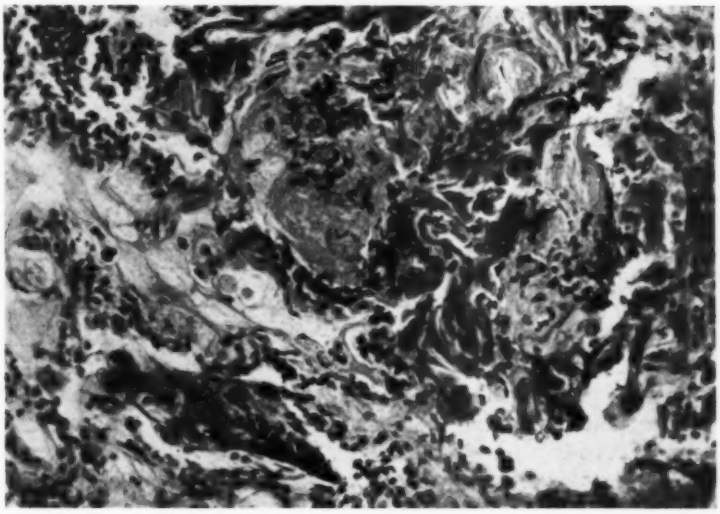

Fig. 6. Squamous-cell carcinoma Aka (No. 167). Killed after 300 r × 15 = 4,500 r. Marked effects of radiation in a tumour partly undifferentiated, partly showing pronounced parakeratosis and cornification.

of varying size, having an eosinophilic protoplasm and showing signs of marked nuclear enlargement and degeneration. Intercellular bridges are never observed after irradiation.

Unlike cellular enlargement, parakeratosis and cornification are unmistakable signs of differentiation, and, unlike GLÜCKSMANN, I consider them the most valuable criteria by which the degree of differentiation in radiated squamous-cell carcinoma can be judged.

The objection may be raised against my experiments that they deal exclusively with morphological changes which do not allow of any conclusions as to the function of the cells. This objection cannot be dismissed without comments, since a histological preparation from a tumour is merely an instantaneous photograph of numerous changing processes and moreover, being fixed and stained, an artificial product, and since microscopic examination shows only certain rough changes in the tumour cells. This applies, however, to all morphological investigations and therefore also to the histological aspect of the concept known as differentiation.

Paying due regard to these objections, *I must conclude from my investigations that therapeutic irradiation of a number of theoretically suitable tumours with roentgen rays and radium is not followed by histo-*

logically demonstrable changes which can be interpreted as criteria of differentiation with our present knowledge of morphology.

In my opinion, the result of my investigations must be that *the dosage in clinical radiotherapy should not be adapted to alterations, if any, in the differentiation during or after the radiation*, as has been advocated by FRIEDMAN (1939—1940). Unlike GLÜCKSMANN and associates, I am of the opinion, based on my studies, *that the histologically demonstrable reaction in a malignant tumour during radiation is inapplicable as a means of foretelling the clinical response of the tumour to the radiation.* In fairly radio-resistant tumours I have often observed cancer cells showing marked effects of the radiation (*e. g.* in certain human mammary tumours and in the spindle-cell sarcoma and chondrosarcoma in mice), and reversely, I have at times found a surprisingly slight histological reaction in tumours which proved to show satisfactory clinical response to radiation (*e. g.* several human basal-cell skin carcinomas and human mammary carcinomas). As far as I can see, *the histological reaction in a malignant tumour during radiation is not a fit standard by which the radiation dose can be adapted.*

This can be done much more safely on the basis of clinical observation of the patient and tumour during radiation.

I am not inclined to think that the histological reaction in a tumour during radiation is a suitable prognostic sign. My material is not, however, applicable in the study of this question, its aim being to investigate the differentiation in malignant tumours on the basis of histological reactions induced by radiation. Therefore, the mouse tumours were studied during or, at most, a few weeks after the radiation, before there was a possibility of recurrences, and the human material was not followed up for a sufficient length of time after the radiation to suggest anything as to the ultimate prognosis. For this end, the human material is also too small and too inhomogeneous.

The histological changes observed in the radiated tumours are in all essentials the same in the various types of tumours, corresponding entirely to the criteria which are generally accepted as signs of cellular degeneration and thus confirm Perthes' and Apolant's theory of degeneration. The cellular changes may frequently be present in a mild degree in areas of spontaneous degeneration in untreated control preparations from the same tumours. To me there is no doubt *that the histologically demonstrable changes in the radiated tumours are signs of degeneration, interpretable as being of non-specific nature, as its individual elements are frequently found, in a milder degree it is true, in the untreated tumours.*

SUMMARY

Therapeutic irradiation of 660 malignant tumours from mice and human beings with roentgen rays and radium failed to produce increased differentiation. The histological changes observed in the radiated tumours are interpreted as a non-specific cellular degeneration.

ZUSAMMENFASSUNG

Therapeutische Bestrahlung von 660 malignen Tumoren an Mäusen und Menschen mit Röntgenstrahlen und Radium rief keine vermehrte Differenzierung hervor. Die in den bestrahlten Tumoren beobachteten histologischen Veränderungen werden als eine unspezifische Zellendegeneration aufgefasst.

RÉSUMÉ

L'irradiation par Rayons de Roentgen et Radium de 660 tumeurs de la souris et de l'homme n'a pas réussi à provoquer une augmentation de la différentiation. Les modifications histologiques observées dans les tumeurs irradiées sont interprétées comme une dégénérescence cellulaire non spécifique.

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PROLAPSE OF REDUNDANT GASTRIC MUCOSA INTO THE DUODENUM[1]

by

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Prolapse of redundant gastric mucosa is a pathological condition which probably SCHMIEDEN (23), in 1911, was the first to draw attention to and describe. His observation was mentioned as a unique occurrence and so well hidden in an extensive paper on differential diagnosis of ulcus and cancer ventriculi, that it was not considered in its true connection until discovered twenty years later by MEYER and SINGER (14). As early as 1925 ELIASON and WRIGHT (5) published a second case without having observed SCHMIEDEN's report.

In America cases of prolapse of redundant mucosa have been described to some extent, whereas in Scandinavia, probably not more than two articles on the subject have been published. In 1947, ZACHO (28), in Denmark, reported two cases diagnosed on operation. In 1949 NYGAARD, AARSETH and LEWITAN (17) wrote an article, based on American material.

In spite of the fact that no more than 30—40 cases have been verified on operation, and that reports on less than twice that number have been published, I have the impression that interest in this question is universal, and not of the kind attached to curiosities. Due to increased knowledge of the characteristic roentgenological symptoms — which at present seem to be the only aid to diagnosis — cases, formerly diagnosed gastritis or neurogenous disturbances, are now expected to be referred to the group of organic diseases.

It may be mentioned, in support of this statement, that SCOTT (24) and NYGAARD and LEWITAN (18), in 1946 and 1948 respectively, found, in a series of roentgenologically examined ventricles, prolapse of re-

[1] Submitted for publication, July 25, 1949.

dundant gastric mucosa in 1 %, and APPLEBY (1) found 7 of these cases among 594 patients subjected to gastric resection. SCOTT (24) says: »In this group of young and adult men, prolapse of the gastric mucosa occurred as often as gastric ulcer.»

The terminology seems to be uncertain. Authors of an early date seem generally to have used terms which refer to prolapse of the gastric mucosa, herniation, intussusception, prolapse or extrusion. ZACHO (28) considers relaxatio tunicae mucosae a very appropriate expression. NORGORE and SHULER (16) point out, and quite rightly, that extrusion is the correct term, from a linguistic point of view. The word prolapse dominates, however, in this respect, as well as in other medical connections of similar character. It does not give rise to misinterpretations, and will be used by the present author.

In the literature redundant prolapsing gastric mucosa is often described under the heading gastric mucosal lesions, *i. e.* it is grouped with benign and malignant tumours. This procedure is not correct, however, although the localization and symptoms of these diseases are fairly similar.

Case Reports

Case 1. Chauffeur, aged 38, having irregular meals, suffered for 9 years from a burning sensation in the epigastrium and acid eructations after meals. In 1944 hyperacidity was established. About X-mas 1946 the disorder increased. The patient had severe epigastric pain 2—3 hours after meals, and cast up 5 bloody vomits in 3 months; he lost 10 kg. in weight during this time.

The patient was admitted to the Medical Department of the Maria Hospital on March 29, 1947. He was given similar treatment as in cases of ulceration of the stomach. Ewald's test meal: Kongo +. There was no blood in the stools. The ventricle was twice roentgenologically examined (the author), with an interval of 3 days. On both occasions fairly regular, arch-shaped defects were observed in the basal part of the bulb. The arches varied in size and shape. Sometimes they were not visible in spite of compression. The pyloric canal was wide, and longitudinal stripes of contrast substance limited the defects which formed direct continuations of the arches in the base of the bulb (Fig. 1). At the first examination the process of evacuation was extremely difficult to set in motion and the peristaltic movements were weak. Three hours and 15 minutes p. c. the ventricle was empty, however. At the second examination the peristalsis was deep and lively, and the ventricle emptied within one and a half hour. As the patient's condition had improved but slightly after treatment covering three weeks, and as the roentgenological examination distinctly favoured prolapse of the gastric mucosa, surgical operation was suggested, but the patient did not accede.

Later the patient was given internal treatment at the Tilkka Military Hospital for five weeks and there was some improvement. In the autumn the patient became worse and was again treated at the same hospital for 3 weeks; he was discharged in good condition. One year later, in autumn of 1948, the patient took up strenuous manual labour. About X-mas he again had severe pain in the epigastrium, practically day and night. This was no doubt due to his hard work. Frequently he vomited during the night.

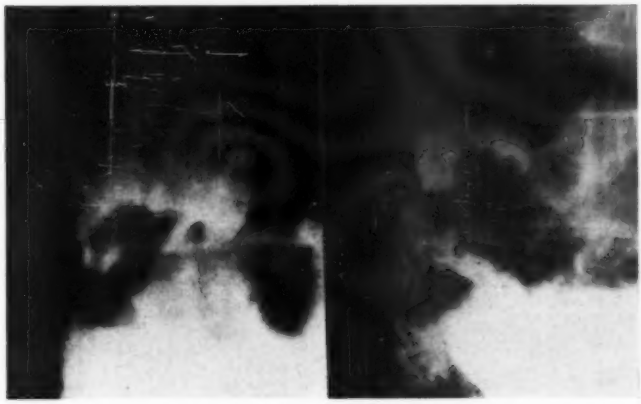

Fig. 1 A. Fig. 1 B.

Fig. 1. Case 1. Pictures of bulb in examination 11.4.47. A. Fairly homogeneous, slightly arched defect in base of bulb. B. Equally broad, parallel rarefaction in pylorus canal and in base of bulb, with characteristic arch-shaped margins.

Fig. 2 A. Fig. 2 B.

Fig. 2. Case 1. Pictures of bulb in examination 3.5.49, *i. e.* 11 days before operation. Arch-shaped defects in base of bulb similar to those in Fig. 1. Very broad pylorus-canal.

The patient was admitted on April 25, 1949 to the Medical Department of the Stengård Hospital and was given internal treatment again for two weeks and a half. April 25: contents of ventricle taken at 9 p. m.: 85 cc., HCl 108, Total acidity 131. April 26: Ewald's test meal: 100 cc. fairly well digested contents of stomach, HCl 77, Total acidity 99. There was no blood in the stools. Two roentgen examinations of the ventricle (Seuderling) showed similar changes in the bulb as two years before (Fig. 2).

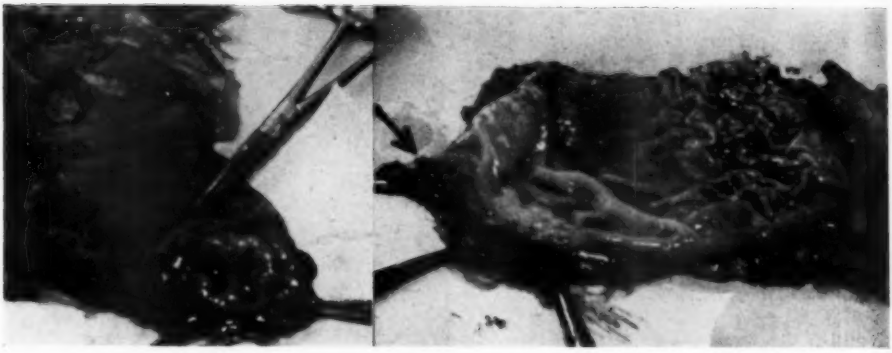

Fig. 3. Fig. 4.

Fig. 3. Case 1. Resected part of ventricle, with folded, mucous membrane prolapsing through pylorus-canal. The forceps attached to margin of bulb.

Fig. 4. Case 1. Opened resection specimen. Arrow indicates collar-shaped, circular wall of mucous membrane, situated immediately oral to pylorus sphincter. Forceps attached to margin of bulb.

On May 11, 1949 the patient was removed to the Finnish Red Cross Hospital for surgical treatment as his condition did not improve at the Stengård Hospital. He still suffered from severe pain, particularly during the night. On May 14 resection of the ventricle was done (IGNATIUS). *To facilitate definite diagnosis of prolapse of the gastric mucosa the surgeon first opened the duodenal bulb, without having been able to palpate anything pathological in the region of the pylorus beforehand. There was no prolapse in fact, but on slight pre-pyloric pressure mucosal folds escaped from the pylorus.* A similar occurrence was observed in the resection specimen (Fig. 3) but the findings in vivo were more distinct. In the opened specimen the prolapsing gastric mucosa appeared in the shape of a circular collar immediately oral to the pylorus sphincter (Fig. 4).

On microscopical examination (Prof. WALLGREN) the glandular tissue was found to be well developed, and the inflammatory changes very slight. This hardly entitles the diagnosis gastritis. The pyloric muscle was strong and there were no signs of fibrosis or other degenerative changes.

One month after the operation the patient was feeling well and had no stomach troubles.

As the roentgenological symptoms in prolapse of the gastric mucosa are fairly characteristic I consider pertinent to report three other cases, in spite of the diagnosis not being verified on operation.

Case 2. Founder, aged 48. Since 1943 the patient had had pain in the epigastrium after meals containing meat, and in particular after eating pork. He also had pain after drinking coffee. Avoiding these food-stuffs the patient felt well. He did not vomit and had no pain during the night. Ewald's test meal: well digested contents of stomach; HCl 50, Total acidity 60. On May 17, 1949 roentgenological examination of ventricle (the author): coarse folds in mucous membrane. Peristalsis deep and rapid; ventricle evacuated in 2 hours; pylorus canal very broad, containing rarefactions of different kinds, probably

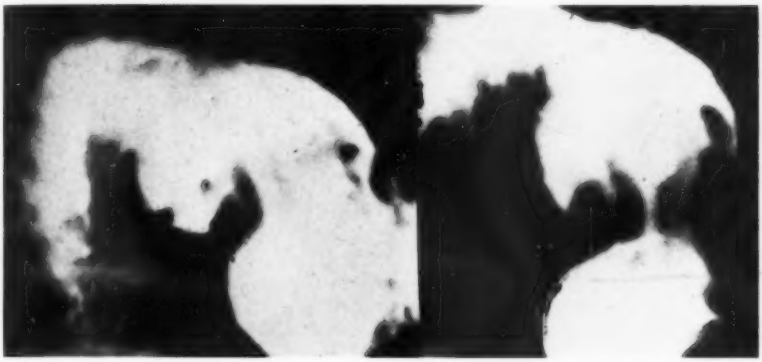

Fig. 5 A. Fig. 5 B.

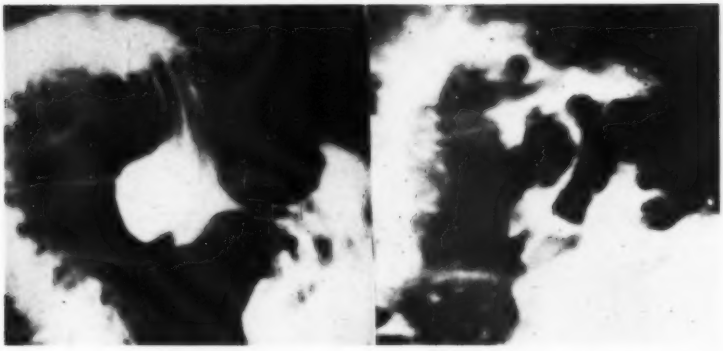

Fig. 5 C. Fig. 5 D.

Fig. 5. Case 2. Roentgen examination of ventricle 17. 5. 49. A. Bulb without compression. Pylorus-canal, very broad, arches in base indistinct. B. Compression somewhat stronger. C. Bulb in process of evacuation. Distinct, longitudinal rarefactions, probably caused by mucosal folds in pylorus-canal and entire basal part of bulb. D. Strong compression. Broad, arch-shaped defects in pylorus and base of bulb.

due to mucosal folds. Rarefactions continue into base of bulb and form arch-like defects, as in Case 1 (Fig. 5). The roentgenological findings suggest prolapse of the mucosa, but as the patient was free from symptoms when keeping strict diet, no operative verification was obtainable.

Case 3. Joiner, aged 54. For 25 years the patient had had stabbing pain in the epigastrium on an empty stomach as well as upon intake of unsuitable food, such as fried food and coffee. This symptom was fairly constant during all these years. By having frequent meals consisting of selected food the patient kept free of symptoms. He did not vomit, and had no pain during the night. Gastric pain sets in after heavy manual work.

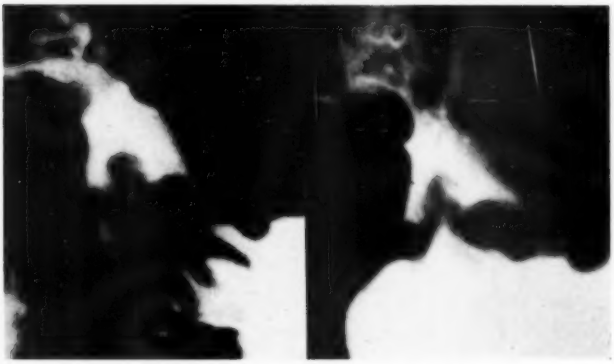

Fig. 6. Case 3. Pictures of bulb in examination 3. 2. 47. In lateral contour a small niche. Round defect close to pylorus-canal, probably caused by prolapse.

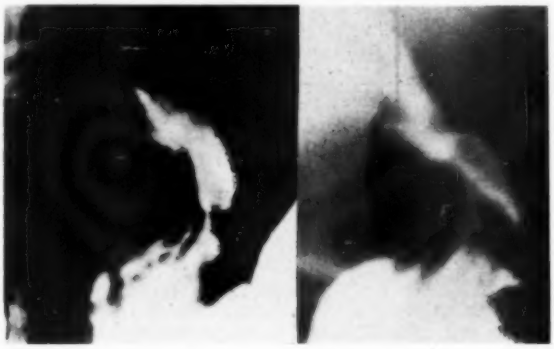

Fig. 7. Case 3. Roentgen examination 21. 6. 49. Bulb slightly deformed. Prepyloric rarefactions which pass through the pylorus and terminate in arches in latero-basal part of bulb.

Ewald's test meal always showed hyperacidity. There was no blood in the stools. On February 3, 1947 roentgenological examination of ventricle (WEGELIUS): severe hypertrophic gastritis in ventricle; niche-formation, suggesting ulcer in lateral recess of bulb (Fig. 6); peristalsis deep and rapid, yet emptying is somewhat retarded. On June 21, 1949 roentgenological examination of ventricle (the author): gastric mucosa of gastritic appearance; pylorus canal broad, within it two longitudinal rarefactions. They start in prepyloric part of ventricle and continue in latero-basal part of bulb which thus cannot fill with contrast substance; their terminations are rounded, they seem to be caused by mucosal folds. Bulb slightly deformed, evidently due to ulcer (Fig. 7). Peristalsis increased, ventricle empties more rapidly than normally. On further study of the pictures taken on February 3, 1947 a rarefaction was observed in the basal part of the bulb, similar to that in prolapse of gastric mucosa. This rarefaction had not been noticed in the first examina-

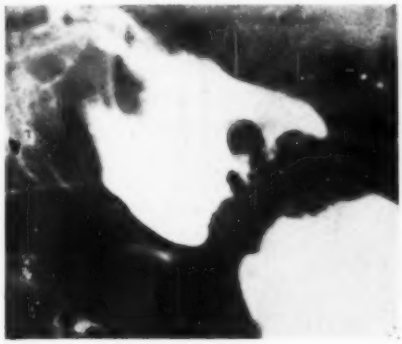

Fig. 8 A.

Fig. 8 B.

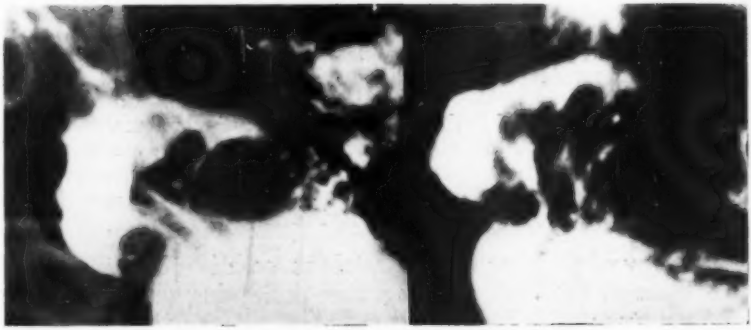

Fig. 8 C.

Fig. 8 D.

Fig. 8. Case 4. Ventricle examination 15. 3. 49. A. Without compression only one large and one small, rounded rarefaction visible close to pylorus in base of bulb. B. Defect divided into three parts, arisen due to slight compression. C. Strong compression. Fairly large basal defect continuing as rarefaction toward the duodenal cap. D. Film taken in angular projection to A, B, C. Large, arch-shaped defects visible in dorso-basal part of bulb.

tion. Thus, a distinct progress has taken place. As there was no reason for surgical intervention the diagnosis cannot be verified.

Case 4. Railway-foreman, aged 57. The patient had had slight pain in the chest and epigastrium for two years, and sometimes acid eructations. He has had extra-systoles to some extent and a difficulty in breathing, He is able to eat all kinds of food. The epigastrium is slightly tender on palpation. Ewald's test meal: 60 cc. badly digested, mucous contents of stomach; HCl 30, Total acidity 45. There was no blood in the stools.

Fig. 9. Small defect close to basal bulb. Probably caused by single gastric ruga.

On March 14, 1949 roentgen examination of the ventricle (the author): mucous membrane of gastritic appearance, in base of bulb variable, fairly large, somewhat irregular defects, resembling a cauliflower (Fig. 8). Peristalsis of ventricle very deep and rapid; empties within 45 minutes. Findings on roentgen examination favour mucosal prolapse. No verification by operation is obtained as the patient is now free of symptoms, following quinidine medication; this suggests that the patient's disturbances were associated with the heart.

Etiology and Pathology

The etiology of prolapse of the gastric mucosa is still not clear. ELIASON and WRIGHT (5) evidently consider prolapsing gastric mucosa an intermediary stage of pedunculated growths and explain the origination of the latter as follows: A low grade inflammation of the mucosa occurs, and a local hypertrophy develops. Contraction of the ventricle ensues which causes the folds to be »pushed along». As the tissue continues to grow it does so at the expence of the stalk. Finally, it is swept into the duodenum by a peristaltic wave.

REES (21) suggests a different mechanism. In three cases operated upon he found »a definite narrowing of the pylorus and an apparent loss of muscular substance. The body of the muscle was white and definitely thinned which would suggest a fibrous degeneration of the muscular tissue.» He considers this narrow, stiff ring the primary cause of this pathological condition. It is followed by hyperperistalsis which loosens the attachement of the mucous membrane to the muscularis in the constricted area. Hypertrophy and prolapse follow, and later polypoid degeneration. These observations are not based on microscopical examinations, and other investigators have not observed similar constriction of the pyloric muscle.

PENDERGRASS (19) points out that anything causing chronic gastritis may lead to prolapse. On patho-anatomical examination BOHRER and COPLEMAN (3) and NORGORE and SHULER (16) found gastritis in surgically treated cases of prolapse.

SCOTT (24) presents a theory in which he claims that gastritis is not the cause of prolapse. In spite of the wall of the ventricle being normal it may occur, in his opinion, when the fibres in the submucosa have become stretched and loosened by abnormal gastric peristalsis due to nervous or chemical stimuli. »A pre-existing disease process is not necessary for the production of a prolapse of the gastric mucosa.»

The patient, described by the present author, subjected to surgical intervention, did not show microscopical changes which might entitle gastritis to be mentioned. Nor did SCOTT (24) find circumstantial evidence. Gastritis cannot thus be considered of determining importance for origination of prolapse; it may, of course, be a phenomenon occurring at the same time.

In his fundamental studies FORSSELL (7, 8) proves distinctly that the motility of the mucous membrane is appreciable. The motility is essentially due to local variations in the filling of the vessels which, in turn, are influenced by the autonomous nervous system. WOLF and WOLFF (27) have shown that emotions may irritate the peristalsis of the ventricle and may change the appearance of the mucous membrane considerably.

In many cases there was a distinct motoric state of irritation in the ventricle. Neurovascular and neuromuscular disturbances may have brought about a tendency to form high mucosal folds. If this condition persists for some time, those, in particular, which lie very close to the pylorus, and are most influenced by the peristalsis, may become permanently redundant. When they have reached a certain size, and increased peristaltic activity, possibly combined with an increased tone in the canalis egestorius, may force them through the pylorus, and prolapse will ensue.

Thus, the author shares the opinion of SCOTT (24). Prolapse of the gastric mucosa takes place by the neurogenous route, through disturbances in the function of the ventricle. The neurogenous connection should be considered more throroughly than hitherto. A diseased process in the ventricle wall is not a condition sine qua non for origination of prolapse.

Symptoms and Clinical Findings

The clinical symptoms are similar to those in gastritis or ulcer, but they do not lead to diagnosis. The physician's thoughts may perhaps be led into the correct channels if the past history of a patient is atypically ulcer-like, or if no response to treatment has been obtained. The disorders

may cause the patient considerable suffering. The effect of dieting is remarkable in Case 2, in spite of hard manual labour, and in Cases 3 and 4, although significant changes were observed on roentgenological examination. There are evidently a number of hidden cases, *i. e.* such in which the prolapse of the gastric mucosa does not affect evacuation unfavourably, and the mucous membrane is normal.

Bockus (2), in his book on »Gastro-Enterology» is no doubt right in saying: »Moderate redundancy of the pyloric mucosa is probably not uncommon but, unless it is associated with severe gastritis or actual prolapse of the gastric mucosa into the duodenum in sufficient quantity to interfere with evacuation of the stomach contents, symptoms are not produced.»

The clinical examination does not as a rule give information of value. The routine laboratory tests may give positive results as regards occult bleeding, probably caused by erosions or stasis due to a tendence to compression. Eliason, Pendergrass and Wright (4) maintain that secondary anemia may occur, and a blood picture, similar to the one in pernicious anemia may be established. The gastric analyses are often normal, notwithstanding hyperacidity and achylia being frequent occurrences.

Diagnosis and Roentgenological Findings

Roentgenological examinations are the only means by which prolapsing redundant gastric mucosa may be diagnosed. The findings are characteristic and when this pathological condition has been revealed the diagnosis, in suspected cases, is without doubt quite simple. The main characteristics are as follows:

1. The prolapsing gastric mucosa causes lobulated filling defects in the basal part of the bulb. In the literature these are termed umbrella- or mushroom-like, or, resembling a cauliflower. The pylorus channel is often very broad, and the course of the prolapsing folds of the mucous membrane can sometimes be followed within it.

2. These filling defects vary in size and shape from one examination to another. They consist of longitudinal rarefactions which are generally equally broad and join corresponding pre-pyloric rarefactions; they terminate in the shape of an arch towards the aboral part of the bulb which is filled with contrast. These rarefactions are separated by thin stripes of contrast which lie in the valleys of the mucous membrane. Visualization is facilitated, and is often dependent almost entirely on the degree of compression required.

Prolapse of the gastric mucosa should not be confused, as pointed out by Scott (24), with a single gastric ruga which normally and frequently

forms a small, central defect in immediate adjacency of the pylorus on the base of the bulb. The small defect in Fig. 9 has probably arisen in this manner.

3. In prolapse of redundant mucosa the peristalsis is generally increased. This is probably due to both these occurrences being an expression for a neuromuscular and neurovascular state of irritation in the wall of the ventricle. The largest defect in the bulb is observed during the stage when the peristalsis has forced the contrast substance into the bulb and evacuation is in progress. The bulb is not »quick» or irritable, contrary to the condition in duodenal ulcer or duodenitis.

4. According to certain authors the prolapse is only visible with the patient in prone position. This is not in agreement with the present author's experience. Erect posture is the best for study of the peristalsis and for finding the suitable degree of compression, and, in consequence, preferable.

5. Fluoroscopy will not suffice for diagnosis of prolapse, as mentioned in a number of papers. This statement concerns every kind of complete roentgen examination of the ventricle and need not be stressed. But, if prolapse is suspected, several films should be taken as the prolapse may vary greatly in appearance.

6. The prolapsing mucosa may be the site of an ulcer (13) — there is even a verified case with malignant changes (22). These circumstances should be taken into consideration as they may confuse the interpretation of the »normal» roentgenological picture of prolapse of the mucosa.

7. No retention was found in my cases — on the contrary, the evacuation was accelerated. Varying reports are found in the literature regarding this question. There is even a statement of a six-hour residue always being present.

Differential diagnosis of prolapse of redundant gastric mucosa affords great difficulties, as mentioned. Judging by the literature this condition has frequently been diagnosed as duodenal ulcer. Lacking knowledge of prolapse of the mucosa is the principal reason for wrong interpretation. Both inveterated and fresh changes in an ulcer are constant, however, and rarely situated in the base of the bulb. Therefore, the diagnosis made by a careful examiner should not be erroneous.

Physicians, confronted with prolapse of pedunculated tumours and polyps (14, 15, 19, 20), have not been able to distinguish them from prolapses of the mucosa. In theory the changes in a polyp should be fairly constant, and there should be no defects resembling mucosal folds, they should be of a more homogeneous character. In papilloma of the duodenum the rarefactions should be large, and not located only in the base of the bulb. Better results may be expected with increased knowledge of the differential diagnostic variations.

Misinterpretation may occur also in hypertrophy of the pyloric muscle. According to KIRKLIN (11) there is a shallow impression of constant shape in the base of the bulb. No filling defects arise on the other hand and this fact should prevent faulty diagnosis.

In duodenitis the base of the bulb may be irregular and may differ from one picture to another. The bulb is, however, very irritable, as already mentioned, and should lead the examiner into the right path.

Furthermore, it should be taken into account that, in oblique view of the base of the bulb, small irregularities in the contour may be found, and a certain striation in the area of the pylorus may be observed, which should not be mistaken for changes of the character of prolapse.

Treatment

Internal therapy, similar to ulcer treatment, is indicated in the first hand, except, of course, in complications involving danger to life, for instance in profuse bleeding from the prolapsing gastric mucosa. In that case surgical therapy has to be resorted to.

Secondary dilatation of the ventricle, caused by obstruction, seems to be very rare. JUDD and MOE's (10) patient had a dilatated, prolonged ventricle, similar to the one in stenosis of the pylorus of prolonged duration. The operation revealed that the prolapsed portion of the mucosa formed almost an occluding diaphragm. No complete »ileus ventriculi» has ever been observed.

If no response is obtained to internal treatment, or if the patient has repeated relapses, surgical operation has to be undertaken. In the majority of the cases excision of the hypertrophic folds and pyloroplasty seems to have been sufficient. REES (21), for instance, recommends antral gastrostomy, excision of the redundant mucosa, anchorage of the mucosa to the muscularis and sectioning of the pyloric muscle.

Cases in which this form of operation has not given results have been described. No response has been obtained in particular in patients with temporary haemorrhage. Partial gastric resection is preferable in such cases. Gastro-enterostomy, performed in two cases, does not seem to be indicated.

The diagnosis cannot be ascertained by palpation of the pyloric area. This should be borne in mind by the surgeon about to operate. The folds of the mucosal membrane may be soft and supple and cannot be palpated. In this connection attention should again be drawn to the fact that in such cases as Case 1 in this paper, the prolapse does not occur until the surgeon presses the pre-pyloric region. The ventricle should always be opened if verification of the diagnosis is aimed at.

SUMMARY

Prolapse of redundant gastric mucosa is a state of disease, to which, in the author's opinion, sufficient attention has not been paid in roentgen diagnosis of the ventricle. The author describes 4 cases, one of which was verified on operation. The diagnosis cannot be made, except by the aid of roentgen rays. In the base of the duodenal bulb limited, arch-like defects, resembling a cauliflower, and varying in size, are observed. The pylorus channel is generally broad, the peristalsis increased, and the evacuation of the ventricle accelerated. Internal therapy should be considered in the first hand. Surgical interference should not be attempted, except in cases with life-threatening haemorrhages, or if frequent relapses have occurred.

ZUSAMMENFASSUNG

Prolaps einer hypertrophischen Magenschleimhaut ist ein Krankenzustand welcher, des Verfassers Ansicht nach, bei der röntgenologischen Ventrikeldiagnostik nicht genug beachtet worden ist. Der Verfasser beschreibt 4 Fälle, von denen einer durch Operation bestätigt ist. Die Diagnose wird durch Röntgenuntersuchung gemacht. Im Basis des Bulbus duodeni entstehen blumenkohlartige bogenförmig begrenzte Defekte von verschiedener Grösse. Der Pyloruskanal ist gewöhnlich breit, die Peristaltik gesteigert und der Magen entleert sich schneller als gewöhnlich. In erster Hand soll interne Therapie versucht werden, bei Rezidiven und lebensdrohende Blutungen wird operiert.

RÉSUMÉ

Prolapse d'une muquese gastrique hypertrophique est une condition pathologique qui d'après l'opinion de l'auteur n'a pas été assez considérée dans le roentgen diagnostic. L'auteur décrit 4 cas, l'un d'eux vérifié par intervention chirurgicale. Le diagnostic est fait aux rayons roentgen. Au bas du bulbe duodenal on voit des formations ressemblant à une tête de chou-fleur, dont les limites sont arquées, de grandeurs différentes. Le canal du pylore est généralement large, la péristaltique est augmentée et l'estomac se vide plus vite que d'habitude. Pour commencer il faut essayer des traitements internes mais en cas de récidives ou de saignements dangereux une intervention chirurgicale est nécessaire.

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